6. SUMMARY AND CONCLUSION

➢ Summary

Cardiometabolic disorders have become a prevalent issue in the modern era of fast paced world. It is represented as a constellation of myriads of metabolic and vascular complications which makes it not only difficult to diagnose but poses challenges for its treatment. Management of CMets includes combination of individual drugs for particular set of complications which leads to inferior outcome, non-adherence and complex PK-PD relationships with prominent adverse effects. To date, medical arena is in search of potent therapeutic interventions that target multiple factors together which leads to the efficient control of the condition.

In order to bridge this gap, current investigation was undertaken to identify novel therapeutic agents for hypertension and CMets that act as multitargeted ligands towards the α_1 and AT_1 receptors. These novel compounds were screened, identified and subsequently studied in appropriate animal models. Firstly, different analogues bearing 6,7-dimethoxyquinazoline and 7,8-dimethozyquinazoline as parent scaffold were scrutinized on rat aortic strip preparation by challenging them against specific agonists like phenylephrine and Ang II for their antagonism on α_1 and AT_1 receptors, respectively. This method allowed the determination of pA_2 values for novel chemical entities which serves as a definitive signal for antagonistic potential of compound and selection for further studies. Results have shown potential of selected scaffold that with appropriate substitution, balanced inhibition can be achieved for the receptors in question. Among screened NCEs, compounds **(11), (18), (21), (24), (42), (48), (80), (82)** were found to exhibit balanced inhibition at both the receptors. Among them, compound **(18)** [pA_2 for $\boldsymbol{\alpha_1}$**=9.47±0.06,** $\boldsymbol{AT_1}$**= 8.54±0.07**] and compound **(24)** [pA_2 for $\boldsymbol{\alpha_1}$**=8.34±0.14,** $\boldsymbol{AT_1}$**= 8.73±0.10**] showed highest and balanced antagonism for α_1 and AT_1 receptors.

Secondly, both compounds were subjected to acute *in-vivo* challenge of phenylephrine and Ang II exhibited pressor response. Despite equivalency in pA_2 values with respect to standard drugs terazosin and losartan, compound **(18)** and **(24)** did not produce significant inhibitory response. Both compounds showed around 50% inhibition while standard drug displayed significant inhibition offering around more than 90% inhibition. These results are not in accordance with tissue study as compound **(18)** and **(24)** showed superior pA_2 values.

To address this inconsistency, it was speculated that by virtue of its dual targeting action, concentration reaching to receptor is not as intended. Hence, NCEs were directed to one receptor while the other receptor was blocked by the standard drug. Data obtained from masked receptor studies revealed significant improvement in the inhibition offered by both compounds i.e., compound **(18)** exhibited around 80% inhibition and compound **(24)** reveled 90% of inhibition of α_1 and AT_1 receptors These results strengthen the efficacy of designed multitargeted ligands for multifactorial disease.

Further, a docking study was conducted to gain insight into the molecular interactions of compounds with targets. Both the compounds were found to display favourable interactions such as hydrogen bonding, pi-pi stacking and salt bridge formation necessary for binding of drugs within the ligand binding domain of α_1 and AT_1 receptors.

Further, in the hierarchical approach of drug discovery, compounds **(18)** and **(24)** were subjected to toxicological evaluation before their intended use in *in-vivo* studies. *In-vitro* toxicity was performed by MTT assay on HEK 293 cells. Results have shown that both compounds are devoid of cell toxicity ranging from 0.1 µM to 1000 µM and IC_{50} of >1000 µM is obtained. *In-vivo* toxicological evaluation by OECD guidelines also revealed no visible toxic signs after administration of single dose of 2000 mg/kg. Study animals showed normal food and water intake and zero mortality was observed during the study period. Gross necroscopy of vital organs also did not reveal any lesion or tissue damage. Thus, it was concluded that both the compounds have LD_{50} value of more than 2000 mg/kg.

After confirming the safety profile of compound **(18)** and **(24)**, they were screened for their drug likeliness properties and ADMET prediction. Compounds were studied by SWISS ADME and pkCSM tool, which are considered as gold standard tool for evaluation of drug likeliness properties. NCEs were evaluated for their druggable properties by Lipinski and Veber's filter and no violations of both the rules were observed. Compound **(18)** and **(24)** displayed excellent logP value of radar chart for maximum allowable limit and also depicted that structural attribute are well within prescribed limit. ADMET prediction also suggested both compounds possess suitable ADMET properties with no structural alerts. Encouraging results obtained from previous study further fuels our investigation and it was decided to evaluate the efficacy of compound **(18)** and **(24)** in UNX+DOCA salt induced hypertension. DOCA salt administration in combination of unilateral nephrectomy produced renin independent form of hypertensive changes in rats exhibited by elevated blood pressure, oedema index, disturbance in urine profile, marked elevation in inflammatory cytokines, accompanied with tissue damage in heart, kidney and aorta.

Treatment of DOCA salt with UNX in rats showed significant elevation in hemodynamic parameters. Compound **(18)** and **(24)** reduced the elevated blood pressure significantly. Treatment with compound **(24)** was found to be superior in comparison to compound **(18)** for reduction of blood pressure. Moreover, it was observed that compound **(24)** produced dose dependent action in reduction of SBP and MABP. Increase in blood pressure was accompanied by overwhelmed vascular reactivity in hypertensive rats. Acute administration of vasoactive agents produced significantly higher response compared to sham control rats. The response of Ang II in hypertension was found to be significantly higher as compared to phenylephrine mediated vasoconstriction. Compound **(18)** and **(24)** produced dose dependent action suggested by more significant inhibition with 10 mg/kg dose. Intercomparison of compounds **(18)** and **(24)** showed only significant difference in MABP reduction where compound **(24)** displayed significant reduction in comparison to compound **(18)**.

Compound **(18)** and **(24)** also prevented endothelial damage inflicted by DOCA salt. Response of Ach mediated relaxation showed significantly less EC_{50} values as compared to DOCA salt rats. Compound **(18)** was found to be more effective than compound **(24)** as evident by more pronounced inhibition offered by compound **(18)** at 10 mg/kg dose and also results are in line with *in-vitro* results of Ach mediated relaxation. UNX + DOCA salt treatment showed significant depletion of NO level which was efficiently restored by 10 mg/kg dose of compound **(18)** and **(24)**. Here, it is important to note that 5 mg/kg dose of novel compounds did not significantly improve plasma nitric oxide level while compound **(18)** at 10 mg/kg produced the highest improvement in the markers of endothelial damage. Treatment with combination of standard drug produced significant but less improvement ascompared to compound **(18)**. These results provide indication of efficiency of dual targetingfor the improvement in cardinal feature of hypertension.

Prominent protection offered by novel compounds led us to gain insight of the molecular mechanism of developed compounds. Significant receptor cross talk exists between α_1 and AT_1 receptors. PKC expression was 4-fold higher in DOCA salt rats. Treatment with compound **(18)** and **(24)** showed significantly less PKC expression in aorta of hypertensive rat. Compound **(24)** at 10 mg/kg produced profound inhibition of PKC expression and it was found to be significantly better in comparison to treatment with compound **(18)**. These results provide insight into overwhelming cross talk and proposed heterodimerization

receptor in response to hypertension. One of key regulators of nitric oxide function, p-Akt was found to be significantly reduced in hypertensive rats where only compound **(24)** at 10 mg/kg produced significant increase in p-Akt level. These results provide conclusive evidence regarding Ach facilitated relaxation by compound **(24)** in *in-vitro* and *in-vivo*.

Persistent hypertension caused significant and remarkable increase in heart and kidney weight. Oedema index was found to be significantly higher in the hypertensive rats where release of cytokines upon persistent hypertension has been studied as a causative factor for the sustenance of hypertension and it was found that UNX+DOCA salt treatment caused cytokine storm characterized by significant elevation in inflammatory cytokines. Hypertensive rats showed 3-fold increase in IL-6 level and 4-fold increase in TNF-α level. Treatment with compound **(18)** at both doses of 5 mg/kg and 10 mg/kg produced significant reduction in cytokine level however, treatment with compound **(24)** at 10 mg/kg showed most significant improvement which is comparable with normal animals. Treatment with standard drug was found to be superior for reducing the IL-6 level. These results are evidence of inhibition of RAAS and SNS together abrogated inflammatory response.

Disturbances in urinary parameters are considered to be hallmark feature of DOCA salt administration. DOCA salt showed significantly less sodium excretion while sodium retention was prevented by concomitant administration of compound **(18)** and **(24).** Both compounds showed similar responses to prevent sodium retention. Compound **(18)** and **(24)** also improved creatinine clearance suggestive of improved kidney function. Treatment with compound **(24)** at 10 mg/kg produced the highest improvement in creatinine clearance. Compound **(24)** was found to be superior in this regard as significant difference was observed between two compounds. Microalbuminuria, as consequence of renal tissue damage was observed in DOCA salt hypertensive rats. Treatment with compound **(18)** and **(24)** was found to be of similar potency. Both compounds showed comparable potency against standard drug treatment by losartan and terazosin. Hence, it was concluded that compound **(18)** and **(24)** provide beneficial effects in amelioration of mineralocorticoid induced hypertension.

Compound **(18)** and **(24)** were found to be preventive against oxidative stress produced by DOCA salt administration. Compound **(18)** and **(24)** offered similar protection again oxidative damage inflicted by UNX+DOCA treatment. Inhibiting overactive alpha adrenergic and RAAS system leads to decreased ROS and RNS generation. Both compounds provided dose dependent protection against oxidative stress. Histopathological

studies also revealed marked inflammation and presence of complex carbohydrate as evident in PAS staining. Treatment with compound **(18)** and **(24)** showed significant improvement in renal architecture. Aortic remodeling was also prevented by treatment with compound **(18)** and **(24)**. Significant improvement in tissue histology was offered by higher dose of compound **(18)** and **(24)** among which compound **(24)** showed significant improvement in tissue architecture in comparison to compound **(18)**.

From the above result, it was concluded that UNX+DOCA salt treatment produced significant alteration in blood pressure, hypertrophic response, disturb the urinary profile with tissue damage. Treatment with novel multitargeted compound **(18)** and **(24)** was found to be beneficial in the prevention of hypertensive changes inflicted by DOCA salt treatment. In comparison of two compounds, compound **(24)** showed better efficacy in terms of blood pressure reduction, improved vascular response and prevention of hypertrophic response after six weeks of DOCA salt treatment.

Further, it was decided to study the preventive potential of compound **(18)** and **(24)** in L-NAME induced hypertension. Chronic blockade by L-NAME generally does not mimic the pathophysiology of human hypertension. However, it is believed to be a suitable model of resistant hypertension. Different studies have reported oral administration of L-NAME for 4 weeks has resulted in a significant increase in blood pressure, however we did not find any change in blood pressure even up to the dose of 60 mg/kg. Therefore, L-NAME was administered at the dose of 15 mg/kg; i.p. along with treatment of compound **(18)** and **(24)** at 5 mg/kg and 10 mg/kg. Physiological parameters such as weight, water intake and food intake showed non-significant changes in either L-NAME or compound **(18)** and **(24)** treated animals.

Significant observations were observed by marked increase in blood pressure by chronic blockade of nitric oxide. L-NAME treatment drastically increased SBP, DBP and MABP after 28 days of treatment. In comparison, compound **(18)** at dose of 5 mg/kg and 10 mg/kg produced significant dose dependent reduction in blood pressure parameters. On the other hand, compound **(24)** also resulted in a significant drop in blood pressure after 28 days of treatment along with L-NAME administration. It was observed that both compounds exhibited almost similar protection marked by non-significant changes between them. Combination of standard drug was found to produce comparable effect with 5 mg/kg dose of compounds in BP reduction. These results shed light on the efficiency of multitargeted

ligands. Heart rate was not changed among study animals in either L-NAME or treatment group. However, standard treatment was found to produce significant bradycardic response in comparison to normal animals which revealed undesired effect obtained with standard drug therapy. Similar observations were also made in case of standard drug therapy group in UNX+DOCA salt induced hypertension suggesting the off-target effect of drugs. It was concluded that multitargeted drug therapy with compound **(18)** and **(24)** produced efficient response in BP reduction at the intended doses with similar degree of benefit in the control of BP.

Hypertrophic response is generated in response to elevated blood pressure meeting the extra demand. However, chronic activation leads to maladaptive changes in heart. Hypertensive rats showed significant increase in heart oedema index while non-significant change was observed for kidney oedema index. Compound **(18)** administered at the dose of 5 mg/kg reduced the heart oedema index however, it was non-significant but higher dose of 10 mg/kg of compound **(18)** produced significant inhibition of maladaptive response in heart. Treatment with compound **(24)** at both the doses were found to be inferior compared to compound **(18)** for the reduction in oedema index.

Ach mediated relaxation and nitric oxide levels showed significant reduction due to L-NAME treatment when compared to normal rats. Ach mediated relaxation was improved in dose dependent manner after treatment with compound **(18)**. Treatment with compound **(24)** also displayed improvement in relaxation mediated by Ach. Here, it is important to note that compound **(18)** produced better relaxation in aortic strip. These results are in accordance with nitric oxide level where compound **(18)** with 10 mg/kg dose significantly increased NO level after 4 weeks of treatment. Treatment with compound **(24)** also exhibited increment in NO level significantly and similar degree of NO level was observed with both novel compounds. Treatment with combination of standard drug also produced significant increase in NO level which was comparable with compounds under investigation.

Next line of evaluation was performed by measuring cytokine level with L-NAME and concomitant treatment with novel compound. Hypertensive rats showed significant increase in IL-6 (0.5-fold) and TNF-α (2-fold) level compared to normal rats. Both the compound **(18)** and **(24)** exhibited significant reduction in mentioned cytokine level in dose dependent manner. It was concluded that dose of 10 mg/kg of novel compounds provides significant protection against L-NAME induced inflammatory response.

Contrary to UNX+DOCA salt model, treatment with L-NAME and investigational compounds did not produce major alteration in urine profile. Non-significant alteration was observed in urine analysis determined by presence of natriuresis, kaluria, uric acid and albumin level. L-NAME administration was marked by oxidative damage in heart and kidney exhibited by significant increment in MDA and decreased GSH level. Compound **(18)** and **(24)** showed dose dependent improvement in oxidative markers. SOD and catalase level were negatively associated with L-NAME treatment. Treatment with compound **(18)** and **(24)** at 10 mg/kg only displayed significant improvement. Treatment with compound **(18)** at 10 mg/kg group offered superior improvement in attaining the balance of oxidative stress markers. It was concluded that compound **(18)** and **(24)** provided noteworthy protection against oxidative damage.

Tissue damage in heart and kidney was evident in response to hypertension in disease control rats when examined under H&E staining. It was characterized by significant presence of inflammatory cells and architectural damage. Treatment with compound **(18)** and **(24)** provides beneficial effects evident via improved histological attributes.

Results shed light on the protective role offered by both newly developed multitargeted ligands. In both compound **(18)** and **(24)**, similar degree of reduction in blood pressure, improvement in endothelial dysfunction, cytokine balance, oedema index and histological changes in tissues was observed. Compounds offered better protection at 10 mg/kg dose for compound **(18)** and **(24)**. Thus, it was concluded that both compounds **(18)** and **(24)** are potential novel multitargeted compounds in hypertension and associated complications in L-NAME induced hypertension caused by chronic nitric oxide inhibition.

Results regarding the efficacy of developed potent multitargeted ligands in hypertension and understanding the role of adrenergic and RAAS in development of insulin resistance and obesity mediated hypertension and cardiometabolic disorders encourage us to expand the role of multitargeted modulation in treatment of CMets.

Along with potent inhibition offered by compound **(18)** and **(24)** for α_1 and AT_1 receptor, compound **(18)** and **(24)** were subjected for their potential interactions with target of CMets. Subsequently they were screened for docking interaction to gain insight regarding their binding and quality of interaction with target. Compounds possess significant interactions with PPARγ receptor and DPP4 enzyme. Interactions of compound **(18)** and **(24)** within active site of SGLT-2 and α-glucosidase did not reveal any specific interactions. Co-crystallized structure of receptor with pioglitazone showed similar binding pocket for

compound **(18)** and **(24)**. Similar observations were made when compound **(18)** and **(24)** were superimposed on co-crystallized structure of DPP4 enzyme with vildagliptin. Favorable interactions such as hydrogen bonding, pi-pi stacking and salt bridge formation were observed which provide significant interactions and drug-target complex stability with protein target.

Further, multitargeted compounds were subjected for their evaluation in cardiometabolic disorders induced by 20% fructose consumption. Fructose induced metabolic alterations are characterized by elevated fasting glucose level and insulin resistance along with elevated TG and decreased HDL level. Compound **(18)** at 10 mg/kg and 20 mg/kg produced a significant decrease in fasting glucose level and dose dependent effect was observed whileboth doses of compound **(24)** were found to significantly decrease the glucose level. Glycemic control showed superior effects of compound **(18)** at 20 mg/kg dose. Combination of standard drug did not reduce glucose level significantly.

Elevated TG levels is one of the consequences of chronic fructose consumption. Compound **(18)** treatment at both intended doses, caused significant reduction in TG level in dose dependent manner and beneficial effect was found to be superior compared to treatment with compound **(24)**.

Treatment with compound **(18)** and **(24)** significantly increased the depleted HDL level due to fructose consumption. Both compounds have increased HDL level in dose dependent manner, however at 20 mg/kg, compound **(18)** showed better reduction of HDL level. Total cholesterol was found to be unaltered after fructose consumption. Neither treatment with compound **(18)** nor **(24)** produced any significant alteration in TC level.

Fructose consumption leads to a marked increase in insulin level accompanied by high glucose level known as “Insulin resistance”. Fructose consumption exhibited significantly increased insulin level. Results are in accordance with evaluation of oral glucose tolerance test. Fructose fed rats showed persistent glucose level even after 4 hours. Treatment with compound **(18)** caused significant reduction in hyperinsulinemia with improved OGTT profile. Treatment with the higher dose of 20 mg/kg was found to provide significant improvement. Compound **(24)** treatment at 10 mg/kg did not show any significant improvement, however, at the dose of 20 mg/kg, animals have shown improved insulin sensitivity marked by significant improvement in insulin and OGTT profile. Surrogate markers of insulin sensitivity also suggested significant improvement with compound **(18)**

and **(24)**. Above data in conjunction with glucose level sheds light on the superiority of multitargeted drugs over standard drug combination.

Fructose feeding caused significant increment in BP marked particularly by SBP and MABP while increase in DBP was found to be insignificant. Compound **(18)** exhibited almost a similar degree of effect for reducing the SBP while dose dependency was observedfor MABP. Treatment with compound **(24)** also significantly reduced MABP in dose dependent manner where dose of 20 mg/kg was found to be more effective for BP control. Administration of 20 mg/kg dose of both novel compounds was correlated with bradycardicor tachycardic response measured by heart rate.

α_1 adrenergic receptor mediated vascular reactivity was significantly higher in diabetic rats. Both the novel compounds by virtue of their α_1 antagonism reduced vascular reactivity significantly. Compound **(18)** was found to be causing dose dependent blockade of α_1 receptors. Treatment with standard drug showed lesser inhibition as compared to compound **(18)**. Ach mediated relaxation was impaired in fructose fed rats; however, it was non-significant when evaluated statistically. Treatment with compound **(18)** and **(24)** at the dose of 20 mg/kg showed marked vasodilation as compared to normal animals. This may be due to the potent inhibition of two major systems offered by novel compounds.

Altered adipocytokine signaling is associated with fructose consumption. However, current study showed non-significant change in adiponectin and leptin level after six weeks of fructose feeding. This may be associated with duration and intensity of fructose feeding. Liver oedema index and heart oedema index were measured as an index of hypertrophic index. Treatment with compound **(18)** and **(24)** resulted into normalization of hypertrophic response in myocardium comparable normal control animals.

The above results shed light on potential of newly developed multitargeted ligands against 20% fructose induced CMets. Both compounds showed beneficial effect in improving cardinal features of Mets characterized by improved glycemic control, reduction in BP and adipocytokine balance. Some features such as metabolic alterations were found to be better controlled by compound **(18)** while BP control was equally managed by compound **(18)** and **(24)**. From the obtained results, it was concluded that targeting RAAS and SNS together provides amelioration of fructose induced CMets. Superiority of novel compoundscan be attributed to its beneficial effects on DPP4 and PPARγ.

The association of hypercoagulability and cardiometabolic disorders is well known. Current investigation is focused on the identification, screening and *in-vivo* study of novel

FXa inhibitors. Last decade has witnessed the therapeutics investigations in field of thromboembolic disorders and FXa remains an attractive target for the development of anti-thrombotic drugs.

The current investigation was performed with a view to search novel FXa inhibitors with improved potency, target specificity and less bleeding risk. Novel compounds bearing 2-aminobenzamide derivatives, 1,3,4-thiadiazole and carbazole derivatives were screened for their FXa inhibitory activity. Among them, compound **(11), (12), (14)** from 2-aminobenzamide derivatives and compound **(47-52, 54, 60)** from 1,3,4-thiadiazole showed excellent IC_{50} values. PT and aPTT time prolongation showed the efficacy of novel compounds in intrinsic and extrinsic pathway of coagulation. Most potent compounds from these series were further selected for *in-vitro* and *in-vivo* studies. Accordingly, compound **(14)** (IC_{50} = 0.7±0.2 µM) and compound **(50)** (IC_{50} = 0.22±0.08 µM) was selected and docking studies showed favorable interactions within active site of FXa enzyme. Compounds **(14)** and **(50)** were further evaluated for their specificity over thrombin viaenzyme inhibition assay. Compound **(14)** and **(50)** possess IC_{50} >80 µM suggestive of absence of binding affinity with thrombin while apixaban showed IC_{50} of 12.8 µM. Compounds under current investigation offer advantages in terms of specificity overthrombin.

Compounds **(14)** and **(50)** were further selected to assess their toxicological concerns before utilizing them for animal experiments. Both compounds showed excellent safety profile depicting IC_{50} value of >1000 µM. Acute administration of compound up to 2000 mg/kg dose did not induce any mortality or allergic reaction or any visible signs of toxic effect of drugs suggestive of safety of developed drugs. Thus, it was considered that compound **(14)**and **(50)** has LD_{50} = >2000 mg/kg.

Excellent *in-vitro* activity with better safety profile of novel molecules encouraged us to study physicochemical and ADMET prediction of compound **(14)** and **(50)**. Compounds were analyzed based on rule presented by Lipinski and Veber. Both compounds were found lying within range prescribed by Lipinski rule of Five. However, violation of limit for TPSA (≤140 $Å^2$) for orally active drug was observed for compound **(50)** where TPSA was found to be 142.45 $Å^2$, but it was still considered within the range. ADMET prediction of compounds **(14)** and **(50)** possess excellent GI absorption characteristics with normal metabolism pathway. Toxicity prediction showed compounds are well tolerated with no

carcinogenic potential except compound **(14)** is predicted to show positive AMES test for mutagenicity.

Compounds **(14)** and **(50)** were further evaluated in *in-vivo* model of arterial thrombosis via $FeCl_3$ and AV shunt induced arterial thrombosis. Evaluation of compound was performed at low dose level, and it was found that both compounds **(14)** and **(50)** showed significant reduction in thrombus weight after $FeCl_3$ application. Compound **(14)** exhibited 25% and 49% inhibition at 15 mg/kg and 30 mg/kg, respectively, while compound **(50)** was found to show 33% and 51% inhibition at 15 mg/kg and 30 mg/kg, respectively. Both compounds exhibited dose dependent reduction in thrombus inhibition and produced almost equable response to standard drug apixaban.

AV shunt induced thrombosis model resulted into significant thrombus formation inside of the cannula. Pretreatment with compounds **(14)** and **(50)** resulted into significant reductionin thrombi weight in dose dependent manner. Compound **(50)** is found to reduce thrombus weight more prominently than compound **(14)**; however, no significant difference was observed. To assess the possible side effects of potential anti-thrombotic drugs, simple tail bleeding model was utilized for primary evaluation of bleeding risk associated with drugs.It was observed that compounds **(14)** and **(50)** showed significantly reduced bleeding time after pretreatment with 15 mg/kg and 30 mg/kg compared to standard drug. This study was limited to thrombus induction and subsequent weight measurement. However, advanced techniques such as Doppler imaging can provide the visual idea of anti-thrombotic action during thrombus formation.

Thus, it was concluded that, compound **(14)** and **(50)** possess excellent IC_{50} value, potent FXa inhibition with high target specificity, better safety and comparable anti-thrombotic action. These compounds can provide potential examples or lead further in development of FXa inhibitors.

➢ **Conclusion**

Cardiometabolic disorders have become a prevalent issue in the modern era of fast paced world. It is represented as a constellation of myriads of metabolic and vascular complications which makes it not only difficult to diagnose but poses challenges for its treatment. Management of CMets includes combination of individual drugs for particular set of complications which leads to inferior outcome, non-adherence and complex PK-PD relationships with prominent adverse effects. To date, the medical arena is in search of potent therapeutic interventions that target multiple factors together which can lead to the efficient control of the condition. In order to bridge this gap, current investigation was undertaken to identify novel therapeutic agents for hypertension and CMets that act as multitargeted ligands towards the α_1 and AT_1 receptors. These novel compounds were screened, identified and subsequently studied in appropriate animal models of hypertension and CMets. Among the library of screened compounds, compound **(18)** and **(24)** were found to provide highest and balanced modulation at both target receptors. Compound **(18)** and **(24)** showed excellent pA_2 value compared to standard drugs and exhibited significant inhibition in phenylephrine (for α_1 receptor) and Ang II (AT_1 receptor) mediated acute pressor response measured by invasive blood pressure. Compound **(18)** and **(24)** also exhibited excellent drug likeliness and safety profile evaluated by SWISS ADME and cytotoxicity assay. Both compounds were evaluated for their in-vivo efficacy in different forms of hypertension, UNX+DOCA salt (cardio renal hypertension) and L-NAME (Nitric oxide inhibition). The compounds showed significant improvement in detrimental changes caused by hypertensive stimuli. Compounds displayed dose dependent pharmacological effects and were found to be superior in abrogating many hypertensive complications compared to combination therapy of standard drugs. We have further expanded our scope of research by realizing the involvement and cross talk of RAAS and adrenergic system in the patho-mechanism of CMets. This led us to test the efficacy of dual antagonists in CMets produced by 20% fructose administration. During the course of the study, we have also explored the affinity of developed compounds with targets of CMets. Compound **(18)** and **(24)** possess significant interactions with PPARγ and DPP4 enzyme. Further, these compounds were subjected against fructose induced cardiometabolic changes. Both the compounds displayed beneficial effect in protection against fructose induced metabolic abnormalities and vascular complications. The protection offered by both compounds was found to be superior than combination of standard drugs, suggesting compound **(18)** and

(24) displayed beneficial effects apart from their dual antagonism i.e. by PPARγ and DPP4 modulatory activity. Another important facet of CMets is hypercoagulability, which is associated with the significant risk of mortality and morbidity in patients. The current investigation was performed with a view to search novel FXa inhibitors with improved potency, target specificity and less bleeding risk. Novel compounds bearing 2-aminobenzamide, 1,3,4-thiadiazole and carbazole scaffolds were screened for their FXa inhibitory activity. Compounds were also evaluated for their PT and aPTT measurement which are clinical markers of antithrombotic treatment. Among screened compounds, two compounds **(14)** and **(50)** from different series were selected for further studies. Both compounds showed potent FXa inhibition along with prolonged PT and aPTT time. This study enables us to identify the potent FXa inhibitors. Further, compounds were explored for molecular interaction within ligand binding domain of enzyme. It was found that both the compounds were able to show beneficial interactions suggestive of its potent inhibitory activity observed in *in-vitro* assays. Results from cytotoxicity study and acute toxicity study showed well tolerated safety profile of drugs and hence, they were further explored in *in-vivo* models of arterial thrombosis by $FeCl_3$ and AV shunt induced arterial thrombosis. Both compounds at the intended dose of 15 mg/kg and 30 mg/kg displayed significant reduction on thrombus formation in dose dependent manner. Assessment of possible side effects of bleeding was evaluated by tail bleeding model, and it was found that compound **(14)** and **(50)** showed a better safety profile than apixaban. Overall, the study unfolds the importance of multitargeted drugs for complex disorders. It is of paramount importance totarget complex and multifactorial diseases with multitargeted drug therapy. This approachis already successfully utilized in treatment of cancer and infections but their role in CMetsand CVDs are still in infancy. The results of the present study indicate that understanding the biological talk between major systems and subsequent modulation by multitargeted drugs can provide safe and efficacious therapeutic alternatives. Targeting FXa for thromboembolic disorders as a cause of CMets and other acquired diseases can provide attractive therapeutic options for treatment. The compounds presented here can provide potential examples or serve as a lead for the future drug development.