Benzofuran–Morpholinomethyl–Pyrazoline Hybrids as a New Class of Vasorelaxant Agents: Synthesis and Quantitative Structure–Activity Relationship Study

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The benzofuran–morpholinomethyl–pyrazoline hybrids 4a–e, 5a–e and 6a–j were synthesized *via* reaction of *α,β*-unsaturated carbonyl compounds 3a–e with hydrazine hydrate, semicarbazide or thiosemicarbazide. Applying the Mannich reaction to 5-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-methoxybenzofuran-6-ols 7a–e with morpholine hydrochloride and paraformaldehyde afforded positional isomeric 7-morpholinomethyl derivatives 4a–e and *N*-morpholinomethyl derivatives 8a–e. All the synthesized compounds showed significant vasodilatation properties in isolated thoracic aortic rings of rats precontracted using the standard norepinephrine hydrochloride technique. Compounds 3d, 3e, 5a–c, 6b, 6c, 6f, 6h and 6i exhibited activity (IC_{50} 0.3185–0.4577 mM) superior to that of prazocin (IC_{50} 0.487 mM), while 5d, 6j and 8c showed comparable activity (IC_{50} 0.4789–0.4951 mM). The quantitative structure–activity relationship study revealed a correlation between the observed vasorelaxant activities of the newly synthesized compounds and their different physicochemical parameters, especially solubility, in addition to structure connectivity and energetic quantities calculated from stored three dimensional (3D) conformations. Absorption, distribution, metabolism and elimination (ADME) evaluation showed good agreement with the biological results obtained.

Key words benzofuran; morpholinomethyl; pyrazoline; vasorelaxant; quantitative structure–activity relationship study

Vasodilators are smooth muscle relaxants which cause blood vessels to dilate. They are prominently used to treat hypertension, heart failure and angina.[1–4] This group of medication is known to cause several undesirable adverse reactions.[5–7] This prompted us to attempt to design and synthesis new effective vasodilators which possess minimal side effects.

Benzofurans are promising candidates for this purpose as they are known found to possess anti-arrhythmic, hypotensive and vasodilator effects.[8,9] The benzofuran amiodarone (**A**) and its analogue KB130015 (**B**) were reported to relax vascular smooth muscle.[10–12] A new noniodinated benzofuran derivative dronedarone, SR33589 (**C**) was recently approved by the Food and Drug Administration (FDA) for treatment of atrial fibrillation and atrial flutter.[13] Khellin (**D**) and visnagin (**E**) are the principle active constituents obtained from *Ammi visnaga* L. and which possess strong vasodilatation and spasmolytic activities.[9,14,15] Some 6-(aminoalkoxy)-5-cinnamoyl-4,7-dimethoxybenzofuran (**F**) derivatives were previously prepared and showed vasodilating and hypotensive activities,[16] (**A**–**F**, Fig. 1).

The morpholine scaffold is very versatile and was featured in a number of biologically and pharmacologically active products such as vasorelaxant,[17] anticancer,[18] antioxidant,[19,20] analgesic,[21] antimicrobial[22,23] and antiparasitic agents.[24]

Mannich bases with morpholinomethyl of synthetic flavonoids exhibited good effects during global ischemia and perfusion in rat brain.[25] In addition, morpholinomethyl benzofurans were reported to exhibit promising hypotensive and antiarrhythimic activities.[26–28] Other Mannich bases, for instance, 7-piperazinomethylbenzofuran derivative showed promising vasorelaxant activity (IC_{50} 0.21 mM) compared with prazocin is (IC_{50} 0.487 mM) in isolated thoracic aortic rings of rats pre-contracted with norepinephrine hydrochloride.[29]

On the other hand, pyrazolines represented a common motif in pharmaceutically and remarkably active compounds demonstrating a wide range of pharmacological activities including anti-inflammatory,[30] analgesic, antitubercular,[31] antimicrobial[32] and antihypertensive agents.[33–35] It was reported that, 4,5-dihydro-1*H*-pyrazole derivatives were potential inhibitors of neural nitric oxide synthase (nNOS) and endothelial cell NOS (eNOS).[36,37] In addition, they played a role in neurotransmission[38] and blood vessel dilation.[39]

In view of the biological significance of benzofuran, morpholinomethyl and pyrazoline, hybrids whose chemical structure incorporated benzofuran directly attached with morpholinomethyl and substituted at 5-position with aryl-4,5-dihydro-1*H*-pyrazoles, compounds **4a**–**e**, **5a**–**e** and **6a**–**j** were synthesized. Compounds **8a**–**e**, benzofuran and morpholinomethyl systems linked through pyrazoline moiety were also synthesized. Generally, the presence of electron-donating groups on the phenyl ring intensifies the biological activities[27–29,40,41] These findings initiated the interest to explore the contribution of methoxy and hydroxyl substituents to the vasorelaxant activity. According to our hypothesis, the combination of two or more biologically active moieties or substituents may bring significant improvement in biological activity and may provide new classes of active vasorelaxant compounds.

Quantitative structure–activity relationship (QSAR) study was also considered in the present work to validate the vasorelaxant activity of the investigated compounds and also for determining the most important structure parameters controlling such activity. Furthermore, drug likeness evaluation of the synthesized compounds as well as prazocin and amioda-

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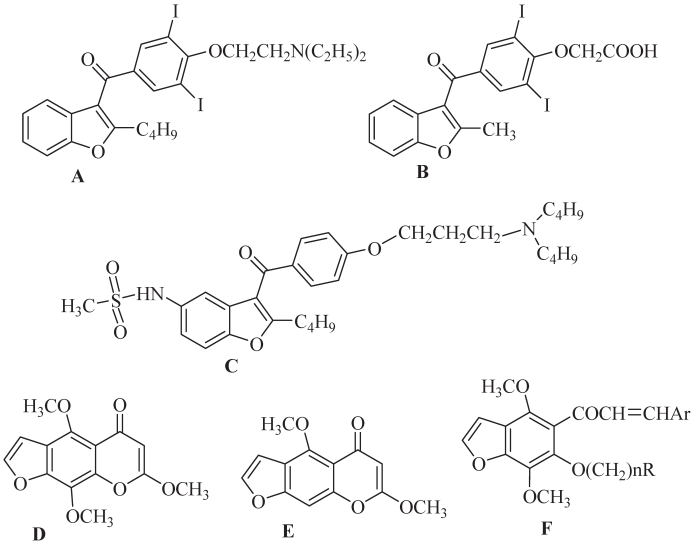
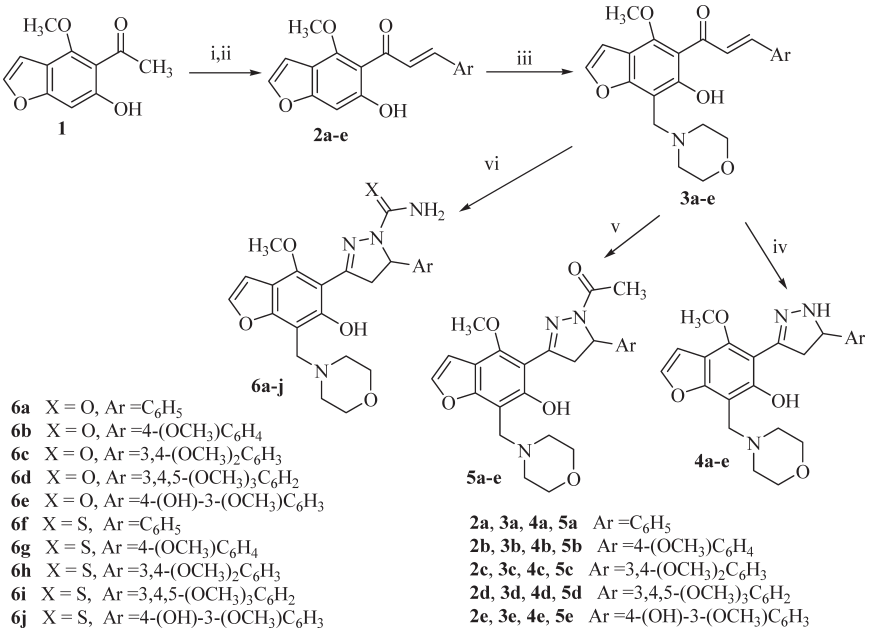


Fig. 1. Structures of Some Benzofurans Have Anti-arrhythmic, Hypotensive and Vasodilator Activities



Reagents and conditions: (i) Appropriate aromatic aldehyde, NaOH, EtOH, rt 48 h, (ii) Acetic acid, (iii) Morpholine hydrochloride, paraformaldehyde, EtOH, reflux, 24 h, (iv) Hydrazine hydrate 98%, EtOH, reflux, 6 h, (v) Hydrazine hydrate 98%, glacial acetic acid, reflux, 6 h, (vi) Semicarbazide or thiosemicarbazide, glacial acetic acid, EtOH, reflux, 8 h.

Chart 1

rone was applied to reveal the relation of molecular properties, structure features and bioavailability of their vasorelaxant activity.

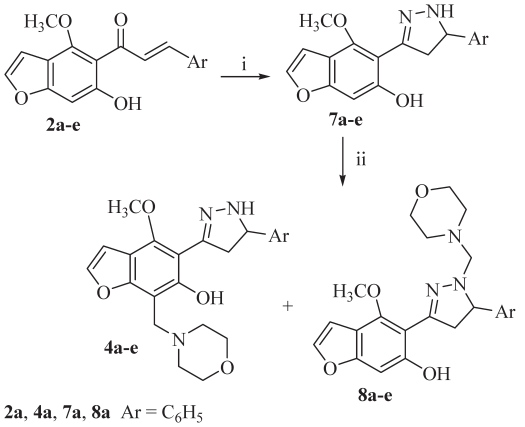
Results and Discussion

Chemistry α,β-Unsaturated carbonyl compounds **2a**,[42] **b**,[43] **c**, **e**[44] and the new **2d** were synthesized by reacting 1-(6-hydroxy-4-methoxybenzofuran-5-yl)ethanone **1**[45] with the appropriate aromatic aldehydes in presence of sodium hydroxide by the conventional Claisen–Schmidt condensation.

On subjecting **2a**–**e** to Mannich reactions using secondary amine (morpholine hydrochloride) and paraformaldehyde, the 7-morpholinomethylbenzofuran derivatives **3a**, **b**,[28] **c**–**e** were formed.

Upon reacting **3a**–**e** with different nucleophiles such as hydrazine hydrate in ethanol, the corresponding pyrazolines **4a**, **b**,[28] **c**–**e** were obtained through 1,4-addition on α,β-unsaturated carbonyl system, followed by dehydration and rearrangement.[43] On the other hand, when **3a**–**e** was reacted with hydrazine hydrate in glacial acetic acid, *N*-acetylpyrazolines **5a**–**e** was obtained. 4,5-Dihydro-1*H*-pyrazole-1-carboxamides **6a**–**e** and 1-carbothioamides **6f**–**j** were obtained through the reaction of **3a**–**e** with semicarbazide or thiosemicarbazide, respectively in ethanol/glacial acetic acid (few drops) (Chart 1).

Similarly, compounds **7a**, **b**[43] and **c**–**e** were prepared starting with compounds **2a**–**e**. Upon reacting 5-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-methoxybenzofuran-6-ol **7a**–**e** with



2a, **4a**, **7a**, **8a** Ar = C_6H_5
2b, **4b**, **7b**, **8b** Ar = 4-$(OCH_3)C_6H_4$
2c, **4c**, **7c**, **8c** Ar = 3,4-$(OCH_3)_2C_6H_3$
2d, **4d**, **7d**, **8d** Ar = 3,4,5-$(OCH_3)_3C_6H_2$
2e, **4e**, **7e**, **8e** Ar = 4-(OH)-3-$(OCH_3)C_6H_3$

Reagents and conditions: (i) Hydrazine hydrate 98%, EtOH, reflux, 3 h, (ii) Morpholine hydrochloride, paraformaldehyde, EtOH, reflux, 24 h, preparative TLC.

Chart 2

morpholine hydrochloride and paraformaldehyde (Mannich reaction), two positional isomers were obtained **4a**–**e** and **8a**–**e**. The later compounds were separated by application of preparative TLC technique (Chart 2).

All the new synthesized compounds were characterized by spectral and elemental analyses which were in full agreement with the proposed structures.

Vasorelaxant Activity All synthesized compounds **3a**–**e**, **4a**–**e**, **5a**–**e**, **6a**–**j** and **8a**–**e** were tested for their vasorelaxant activities against nor-adrenaline-induced spasm on thoracic rat aorta rings[46–48] and were compared to the reference drug, prazocin. The results are listed in Table 1 and illustrated in Fig. 2 as IC_{50} values (mM). These results exhibited the correct choice of compounds' design as hybrids of benzofuran scaffold with morpholinemethyl and pyrazoline as vasorelaxant agents as all the tested compounds showed biological activity.

Regarding the morpholinomethylbenzofuran chalcones **3a**–**e**, substitution of phenyl ring with methoxy and hydroxyl substituent, (compound **3e**, IC_{50} 0.3185 mM) followed by trimethoxy substitution (compound **3d**, IC_{50} 0.4577 mM) gave better vasorelaxant activity than reference drug prazocin (IC_{50} 0.487 mM) as expressed by lower IC_{50} values. Unsubstituted, monomethoxy and dimethoxy substituted compounds gave activity less than prazocin (IC_{50} 0.6585, 0.5069 and 0.5342 mM, respectively). This was in agreement with previous reports of vasorelaxant activity of the chalcone system.[49–51]

Cyclization of compounds **3a**–**e** to produce pyrazoline derivatives **4a**–**e** resulted in slight decrease in activity as expressed with increase in IC_{50} values (IC_{50} 0.5502–0.7625 mM).

On the other hand cyclization of compounds **3a**–**e** to produce *N*-acetylpyrazoline **5a**–**e**, pyrazoline carboxamide **6a**–**e**, pyrazoline carbothioamide **6f**–**j** derivatives resulted in improvement of activity for most compounds. Results of *N*-acetylpyrazolines **5a**–**e** revealed that compounds **5a**–**c** (IC_{50} 0.4171, 0.4550 and 0.3704 mM, respectively) showed better activity than prazocin while compound **5d** (IC_{50} 0.4951 mM) was comparable to prazocin and compound **5e** (IC_{50} 0.5340 mM) was slight less active than prazocin. In case of pyrazoline carboxamide derivatives **6a**–**e**, compounds **6b** and **c** (IC_{50} 0.4475 and 0.4158 mM, respectively) showed activity better than prazocin while compounds **6a**, **d** and **e** (IC_{50} 0.6332, 0.5564 and 0.5243 mM, respectively) were less active than prazocin. Carbothioamide derivatives **6f**–**j** exhibited better vasorelaxant activity than carboxamide derivatives **6a**–**e** as expressed with lower IC_{50} values for most compounds. Compounds **6f**, **h** and **i** (IC_{50} 0.4212, 0.4041 and 0.3505 mM, respectively) showed better activity, while compound **6j** (IC_{50} 0.4789 mM) was comparable to prazocin and compound **6g** (IC_{50} 0.5815 mM) was less active than prazocin.

Table 1. Concentration of Compounds Necessary to Reduce Maximal Norepinephrine-Induced Contracture by 50% (IC_{50}) in Rat Thoracic Aortic Rings

Compd. No.	IC_{50} (mM)
3a	0.6585
3b	0.5069
3c	0.5342
3d	0.4577
3e	0.3185
4a	0.7625
4b	0.5502
4c	0.5664
4d	0.6021
4e	0.5748
5a	0.4171
5b	0.4550
5c	0.3704
5d	0.4951
5e	0.5340
6a	0.6332
6b	0.4475
6c	0.4158
6d	0.5564
6e	0.5243
6f	0.4212
6g	0.5815
6h	0.4041
6i	0.3505
6j	0.4789
8a	0.7657
8b	0.6681
8c	0.4937
8d	0.6916
8e	0.8022
Prazocin	0.4870

As for positional isomer *N*-morpholinomethlypyrazolines **8a**–**e**, vasorelaxant activities were less than their isomers **4a**–**e**. Except compound **8c** (IC_{50} 0.4937 mM) which exhibited activity comparable to prazocin and the rest of compounds **8a**, **b**, **d** and **e** (IC_{50} 0.6681–0.8022 mM) were less than prazocin.

Structure Activity Relationship Examination of the vasorelaxant activity results revealed that separation of morpholinomethyl moiety from benzofuran scaffold by pyrazoline spacer (compounds **8a**–**e**) resulted in decrease in activity compared to their positional isomers **4a**–**e** where morpholinomethyl moiety was directly linked to benzofuran scaffold.

Morpholinomethylbenzofuran chalcones **3a**–**e** gave good vasorelaxant activity but cyclization to pyrazoline derivatives **4a**–**e** resulted in slight decrease in activity while cyclization to *N*-acetylpyrazoline **5a**–**e**, pyrazoline carboxamide **6a**–**e**, pyrazoline carbothioamide **6f**–**j** derivatives resulted in improve-

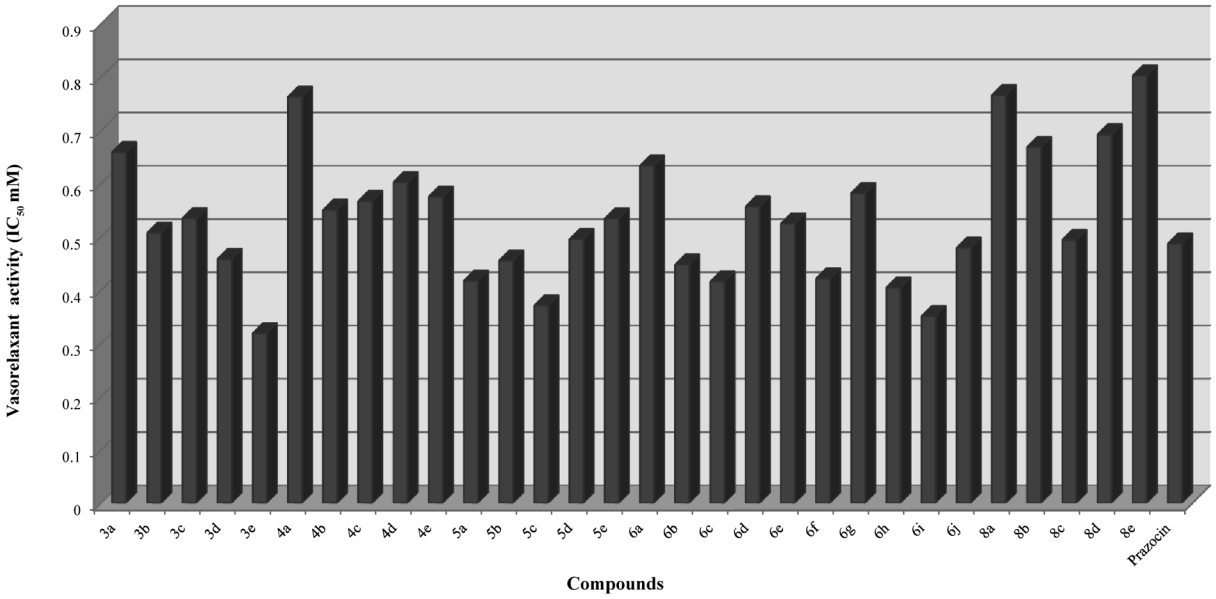


Fig. 2. Vasorelaxant Activity (IC_{50} Values) of Tested Compounds on Contracture Induced by Norepinephrine Hydrochloride on Thoracic Rat Aortic Rings Compared to Prazocin

ment of activity for most compounds.

N-Acetylpyrazoline derivatives **5a–e** exhibited highest activity followed by pyrazoline carbothioamide **6f–j** then pyrazoline carboxamide derivatives **6a–e** while pyrazoline derivatives **4a–e** were the least active among this class of compounds.

In addition, the influence of methoxy and hydroxyl substituted aryl pyrazolines on the vasorelaxant activity was observed. At least one methoxy group substitution was essential to increase vasorelaxant activity compared to unsubstituted ring. The effect was increased with the second methoxy substituent and to a lesser extent with additional two methoxy or one hydroxyl group substitution.

QSAR In order to correlate the vasorelaxant activity expressed as log IC_{50} (mM) with the structure conformation of the synthesized benzofuran–morpholinomethyl–pyrazoline hybrids, QSAR study was undertaken. The study was performed using MOE, Molecular Operating Environment software package (MOE version 2008.10.2).[52]

Different molecular descriptors (Table 2) were selected from an initial pole of 85 descriptors and were calculated for compounds structure aiming to cover a wide range of different electronic, hydrophobic and topological characters. In order to avoid multicolinearity between the calculated descriptors the correlation matrix was calculated. The correlation matrix indicated that some of the descriptors used were highly correlated which suggests avoiding the combinations of such intercorrelated descriptors.

Model Construction To test the best structural predictors for activity, stepwise linear regression analysis (SLRA) technique was used.

For the current dataset of 30 compounds, the QSAR model was derived by partial least square. The development of QSAR model was restricted to a maximum of four variables in accordance the general accepted rule for each compound: descriptors ratio to be around 5 : 1.

The simple linear regression analysis between the log IC_{50} and the different descriptors yields one statistically significant correlation (Model 1), that was the correlation between the activity (log IC_{50}) and the log S of the tested compounds. Compounds **3e** and **6g** were omitted as outliers while deriving

Table 2. The Molecular Descriptor Values of the Studied Compounds

Compd. No.	Descriptors			
	log S	VSA	E_sol	rgyr
3a	−5.2602	415.3450	−5.9096	4.2836
3b	−5.3106	444.1414	−10.1487	5.0438
3c	−5.3610	474.1896	−2.9714	5.3157
3d	−5.4113	501.4015	0.8602	5.0932
3e	−4.9486	449.5437	−11.8534	5.1419
4a	−4.5772	419.5661	−8.8021	4.6045
4b	−4.6276	456.8181	−12.0295	4.9362
4c	−4.6780	490.1929	−12.9473	5.0422
4d	−4.7283	517.1149	−7.6016	5.0507
4e	−4.2656	464.8755	−8.8987	4.8255
5a	−5.0658	468.3897	−9.5429	4.4384
5b	−5.1161	496.8009	−20.3672	4.5314
5c	−5.1665	529.1497	−6.8252	4.8810
5d	−5.2169	560.5244	−6.9133	4.8320
5e	−4.7542	503.4925	−16.6703	4.6650
6a	−5.0056	461.2488	−8.5186	4.4359
6b	−5.0560	494.3793	−11.8881	4.7452
6c	−5.1064	524.4553	−14.3439	4.8093
6d	−5.1568	549.1744	−11.8380	4.6072
6e	−4.6940	496.1378	−26.7391	4.5096
6f	−6.0407	471.0862	2.8766	4.4424
6g	−6.0911	506.7375	−7.9529	4.7773
6h	−6.1414	530.6677	−3.5103	4.8021
6i	−6.1918	562.1160	−2.2115	4.7922
6j	−5.7291	507.7466	−4.5232	4.7679
8a	−4.3847	426.4172	−7.7219	4.3002
8b	−4.4351	459.0730	−9.0937	4.4039
8c	−4.4855	490.3040	0.6237	4.6997
8d	−4.5359	519.6377	5.5265	4.7292
8e	−4.0732	462.5117	−3.2103	4.5672

the model. Detection of outliers was achieved through the Z score method. Z Score can be defined as absolute difference between the value of the model and the activity field, divided by the square root of the mean square error of the data set. Any compound which shows a value of Z score higher than 2.5, during generation of a particular QSAR model, is considered as an outlier.[53]

$$\log IC_{50} = 3.35834 + 0.12660 \times \log S$$
$$n = 28,\ \mathrm{RMSE} = 0.06457,\ r^2 = 0.5279 \quad \text{(Model 1)}$$

n: number of compounds used for construction of model. RMSE: root mean square error. r^2: correlation coefficient.

Stepwise regression analyses using different combinations of log S and other structural descriptors resulted into bi-parametric model (Model 2). The biparametric model correlated vasorelaxant activity ($\log IC_{50}$) with log S and VSA. Model 2 showed better statistics than the mono-parametric model discussed above. Compounds **5a** and **c** were omitted as outliers while deriving the model.

$$\log IC_{50} = 3.63093 + 0.09961 \times \log S - 0.00082 \times \mathrm{VSA}$$
$$n = 26,\ \mathrm{RMSE} = 0.04983,\ r^2 = 0.6934 \quad \text{(Model 2)}$$

Stepwise regression analyses using different combinations of log S and VSA with other structural descriptors resulted in tri-parametric model (Model 3). The triparametric model correlated $\log IC_{50}$ with log S, VSA and E_sol. Model 3 exhibited better statistics than the mono-parametric and biparametric models discussed above. Compounds **6d** and **8c** were omitted as outliers while deriving the model.

$$\log IC_{50} = 3.79347 + 0.12247 \times \log S - 0.00084 \times \mathrm{VSA} + 0.00409 \times \mathrm{E\_sol}$$
$$n = 24,\ \mathrm{RMSE} = 0.03662,\ r^2 = 0.8459 \quad \text{(Model 3)}$$

Stepwise regression analyses using different combinations of $\log IC_{50}$ with log S, VSA & E_sol with other structural descriptors resulted into tetraparametric model (Model 4). The tetraparametric model correlated $\log IC_{50}$ with $\log IC_{50}$ with log S, VSA, E_sol and rgyr. Model 4 revealed better statistics than the other models discussed above. Compounds **4e** and **6f** were omitted as outliers while deriving the model.

$$\log IC_{50} = 4.05175 + 0.12029 \times \log S - 0.00080 \times \mathrm{VSA} + 0.00502 \times \mathrm{E\_sol} - 0.05864 \times \mathrm{rgyr}$$
$$n = 22,\ \mathrm{RMSE} = 0.0287,\ r^2 = 0.9074 \quad \text{(Model 4)}$$

The $\log IC_{50}$ (observed) was plotted against their predicted values (MLR), Table 3 and Fig. 3.

From the obtained regression equation, vasorelaxant activity was positively correlated (*i.e.*, directly proportional) with log S (physical properties descriptor) and with E_sol (potential energy descriptor, used to calculate energetic quantities from stored 3D conformations) and negatively correlated (*i.e.*, inverse proportional) with rgyr and VSA (surface area, volume and shape descriptors which depend on the structure connectivity and conformation). The high coefficient value of log S and the comparatively lower value of E_sol, rgyr and VSA suggested that the increase in aqueous solubility of the compound lead to enhancement of activity. This was in good agreement with Jorgensen's rule of three (log $S_{wat} > -5.7$),[54] which is considered essential for bioavailability. All tested compounds were in compliance with this rule except compounds **6h** and **i** that had slight lower log S −6.1414 and −6.1918, respectively but this compensated with low value of rgyr and VSA descriptors (compounds **6f** and **g** were considered outliers). QSAR results assured that the aqueous solubility of the compounds is one of the most important determinants for the vasorelaxant activity due to increase in bioavailability.

Cross-Validations Test Normal and cross-validation statistical techniques were applied to estimate the quality with regards to predictive ability of the generated Model 4 (Table 3) using MOE software. In the cross validation technique, where a number of modified data sets were created by deleting, in each case, one or a smaller group of objects from the data in such a way that each object was taken away once and only once. For each reduced data set, the model was calculated, and responses for the deleted objects were predicted from the model. The simplest and most general cross-validation procedure is the leave-one-out technique (LOO technique), where each object of the data set is taken away, one at a time.

q^2 (leave-one-out)=0.860459, it was calculated by the following equation[53]:

$$q^2 = 1 - \frac{\sum (IC_{50}\,\mathrm{Obs.} - IC_{50}\,\mathrm{Pred.})^2}{\sum (IC_{50}\,\mathrm{Obs.} - IC_{50}\,\mathrm{average})^2}$$

The $\log IC_{50}$ (observed) was plotted against their predicted values (LOO), Table 3 and Fig. 4.

Statistical Diagnosis Fraction of the Variance (r^2): Represent the goodness of fit. The value of r^2 may vary between 0 and 1, when multiplied by 100 gives explanation to variance in biological activity, where 1 means a perfect model explaining 100% of the variance in the data, and 0 means a model without any explanatory power. It has already been suggested that the only QSAR model having $r^2 > 0.6$ will be considered for validation.[55] The value of r^2 for this QSAR model is 0.9074.

Cross-Validation Test (q^2): A measure of quality of the QSAR model. According to the literature, a QSAR model must have $q^2 > 0.5$ for their predictive ability.[55] The value of q^2 for this QSAR model is 0.860459.

$r^2 - q^2 < 0.3$: This difference between r^2 and q^2 for a QSAR model should never be exceeded by 0.3. A large difference between r^2 and q^2 suggests the following: over-fitted model, presence of outliers or presence of irrelevant variables in the data set.[56] The value of $r^2 - q^2$ for this QSAR model is 0.113541.

ADME Evaluation As a part of our study, the compliance of the benzofuran drug amiodarone, reference drug prazocin and the synthesized compounds with the Lipinski's rule of five[57] was evaluated. This was assessed using mipc—Molinspiration Property Calculator.[58]

Lipinski's rule had been used in the evaluation of oral bioavailability of the compounds. Lipinski's rule of five defines molecular properties important to the drug's pharmacokinetics in the human body, including their (ADME) and is used to insure that drug-like physicochemical properties. The rule describes a likely oral bioavailability molecule as (i) a molecular weight (MW) less than 500 Daltons (Da), (ii) the logarithm of the octanol/water partition coefficient representing the lipophi-

Table 3. The Experimental and Predicted Activities ($\log IC_{50}$), Residuals and *Z*-Scores for the Tested Compounds Calculated Using MLR Validation and the Corresponding Cross-Validation LOO

Compd. No.	log Obs. IC_{50}	MLR validation			LOO validation		
		log Pred. IC_{50}	Residual	*Z*-Score	log Pred. IC_{50}	Residual	*Z*-Score
3a	2.8190	2.8063	0.0127	0.4412	2.7980	0.0210	0.7195
3b	2.7050	2.7114	−0.0064	0.2240	2.7140	−0.0090	0.3084
3c	2.7280	2.7014	0.0266	0.9261	2.6874	0.0406	1.4240
3d	2.6610	2.7059	−0.0449	1.5642	2.7160	−0.0550	2.0148
4a	2.8820	2.8518	0.0302	1.0522	2.8454	0.0366	1.2875
4b	2.7410	2.7803	−0.0393	1.3705	2.7879	−0.0469	1.6828
4c	2.7530	2.7368	0.0162	0.5645	2.7332	0.0198	0.6800
4d	2.7800	2.7355	0.0445	1.5488	2.7258	0.0542	1.9813
5b	2.6580	2.6715	−0.0135	0.4717	2.6752	−0.0172	0.5888
5d	2.6950	2.6584	0.0366	1.2760	2.6483	0.0467	1.6715
5e	2.7280	2.7204	0.0076	0.2632	2.7193	0.0087	0.2972
6a	2.8020	2.7783	0.0237	0.8266	2.7750	0.0270	0.9351
6b	2.6510	2.7107	−0.0597	2.0803	2.7144	−0.0634	2.4265
6c	2.6190	2.6645	−0.0455	1.5867	2.6710	−0.0520	1.8976
6e	2.7200	2.6922	0.0278	0.9698	2.6752	0.0448	1.5796
6h	2.6060	2.5898	0.0162	0.5632	2.5840	0.0220	0.7571
6i	2.5450	2.5658	−0.0208	0.7230	2.5769	−0.0319	1.1065
6j	2.6800	2.6547	0.0253	0.8826	2.6506	0.0294	1.0216
8a	2.8840	2.8927	−0.0087	0.3046	2.8954	−0.0114	0.3893
8b	2.8250	2.8476	−0.0226	0.7887	2.8516	−0.0266	0.9205
8d	2.8400	2.8414	−0.0014	0.0485	2.8425	−0.0025	0.0845
8e	2.9040	2.9084	−0.0044	0.1520	2.9100	−0.0060	0.2035

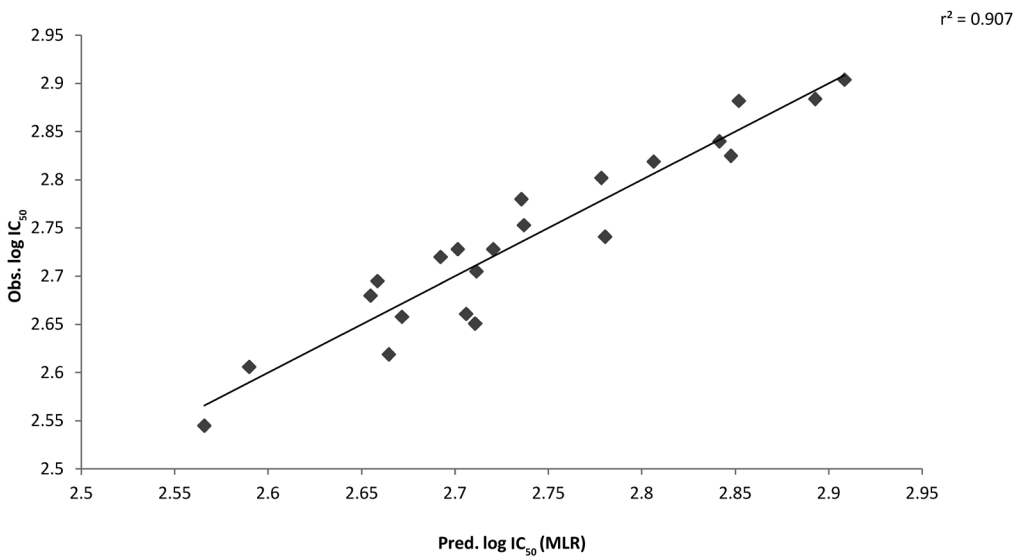


Fig. 3. Correlation of log Observed and log Predicted IC_{50} Using MLR (r^2=0.9074)

licity factor (log*P*) less than 5, (iii) not more than 5 hydrogen bond donors (OH and NH groups, HBD), (iv) not more than 10 hydrogen bond acceptors (HBA) and (v) not more than 10 rotatable bonds (NRB). The number of violation to this rule must not exceed 2 and at least three parameters coincide with the rule.[57] In addition, the topological polar surface area (TPSA) of the compounds was also calculated since it is another key property that has been linked to drug bioavailability, TPSA equal to or less than 140 $Å^2$ are considered to have good oral bioavailability.[59] Absorption and liver first-pass metabolism determine the bioavailability of a compound.[54] Absorption depends on solubility and permeability of the compound and interactions with metabolizing enzymes in the gut wall while functional group types present are responsible for metabolism.

According to Jorgensen's rule of three, the computed parameters used to assess oral absorption should comply with the following values ($\log S_{wat} > -5.7$, $BIP_{caco\text{-}2} > 22$ nm/s and primary metabolites <7) to be orally available. The most important parameters considered are the predicted aqueous solubility, $\log S_{wat}$.[54]

The size of a molecule, lipophilicity, capacity to make hy-

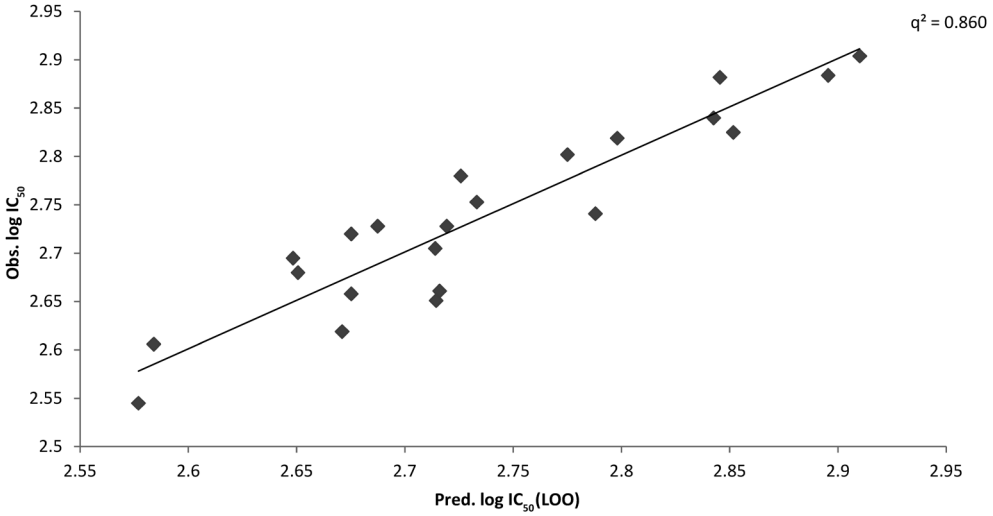


Fig. 4. Correlation of log Observed and log Predicted IC_{50} Using LOO (q^2=0. 860459)

Table 4. ADME of the Synthesized Compounds Using Mipc—Molinspiration Property Calculator

Compd. No.	TPSA	MW	mi log *P*	HBA	HBD	NRB	No. of violation
3a	72.145	393.439	3.384	6	1	6	0
3b	81.379	423.465	3.44	7	1	7	0
3c	90.613	453.491	3.03	8	1	8	0
3d	99.847	483.517	3.015	9	1	9	0
3e	101.607	439.464	2.723	8	2	7	0
4a	79.465	407.47	2.89	7	2	5	0
4b	88.699	437.496	2.946	8	2	6	0
4c	97.933	467.522	2.536	9	2	7	0
4d	107.167	497.548	2.521	10	2	8	0
4e	108.927	453.495	2.229	9	3	6	0
5a	87.747	449.507	2.496	8	1	5	0
5b	96.981	479.533	2.552	9	1	6	0
5c	106.215	509.559	2.142	10	1	7	1
5d	115.449	539.585	2.127	11	1	8	2
5e	117.209	495.532	1.835	10	2	6	0
6a	113.77	450.495	2.41	9	3	5	0
6b	123.004	480.521	2.467	10	3	6	0
6c	132.238	510.547	2.057	11	3	7	2
6d	141.472	540.573	2.042	12	3	8	2
6e	143.232	496.52	1.749	11	4	6	1
6f	96.699	466.563	2.951	8	3	6	0
6g	105.933	496.589	3.008	9	3	7	0
6h	115.167	526.615	2.598	10	3	8	1
6i	124.401	556.641	2.583	11	3	9	2
6j	126.161	512.588	2.29	10	4	7	1
8a	70.676	421.497	3.797	7	1	5	0
8b	79.91	451.523	3.853	8	1	6	0
8c	89.144	481.549	3.443	9	1	7	0
8d	98.378	511.575	3.428	10	1	8	1
8e	100.138	467.522	3.136	9	2	6	0
Amiodarone	42.683	645.319	8.31	4	0	11	2
Prazocin	106.962	383.408	1.909	9	2	4	0

TPSA: Topological polar surface area. MW: Molecular weight. mi log *P*: Octanol–water partition coefficient (predicted log *P* at molinspiration). HBA: No. of H-bond acceptors. HBD: No. of H-bond donors. NRB: No. of rotatable bonds.

drogen bonds as well as shape and flexibility are important properties to consider when determining its oral bioavailability.[59]

The calculated parameters (Table 4) showed good bioavailability of studied compounds. Most compounds fulfilled Lipinski's rule similar to the clinically used drug prazocin. Compounds **5c**, **6h**, **j** and **8d** violated the rule of five in molecular weight value while compounds **5d**, **6c** and **i** violated

in molecular weight value and HBA. In addition, compound **6e** violated in HBA and had slightly large TPSA (143.232 Å^2). Also, compound **6d** violated in molecular weight value and HBA and had slightly large TPSA (141.472 Å^2). Meanwhile, amiodarone violated in molecular weight value and log*P*. Hence; theoretically, all of these compounds should present good passive oral absorption and differences in their bioactivity cannot be attributed to this property.

Conclusion

This study describes the design and synthesis of new benzofuran–morpholinomethyl–pyrazoline hybrids as vasorelaxant agents. All the synthesized compounds showed significant vasodilatation properties using isolated thoracic aortic rings of rats pre-contracted with norepinephrine hydrochloride standard technique and results were compared with reference drug prazocin. Results revealed that direct linked morpholinomethyl moiety to benzofuran scaffold **4a**–**e** gave better results than their positional isomers **8a**–**e** with morpholinomethyl moiety separated away from benzofuran scaffold by pyrazoline spacer. *N*-Acetylpyrazoline derivatives **5a**–**e** exhibited highest activity followed by pyrazoline carbothioamide **6f**–**j** then pyrazoline carboxamide derivatives **6a**–**e** while pyrazoline derivatives **4a**–**e** were the least active among this class of compounds. In general, methoxy and hydroxyl substitution on the phenyl ring at pyrazoline had good effect on activity.

In addition QSAR and drug likeness studies results accounted for the importance of aqueous solubility on oral bioavailability and activity of tested compounds.

Experimental

Chemistry Melting points were determined by open capillary tube method using Gallen Kamp melting point apparatus MFB-595-010M (Gallen Kamp, London, U.K.) and were uncorrected. Microanalyses were carried out at The Regional Center for Mycology and Biotechnology, Al-Azhar University. Infrared spectra were recorded as potassium bromide discs on Schimadzu FT-IR 8400S spectrophotometer (Shimadzu, Kyoto, Japan) and expressed in wave number (cm^{-1}). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in deuterated chloroform ($CDCl_3$). Chemical shifts are quoted in δ as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were recorded using Hewlett Packard Varian (Varian, Polo, U.S.A.) and Shimadzu Gas Chromatograph Mass spectrometer-QP 1000 EX (Shimadzu). TLC were carried out using Art.DC-Plastikfolien, Kieselgel 60 F254 sheets (Merck, Darmstadt, Germany), the developing solvents were chloroform/methanol (9 : 1) and the spots were visualized at 366, 254 nm by UV Vilber Lourmat 77202 (Vilber, Marne La Vallee, France).

Compounds **1**,[45] **2a**,[42] **b**,[43] **c**, **e**,[44] **3a**, **b**, **4a**, **b**,[28] **7a** and **b**[43] were prepared according to reported procedures.

General Procedure for Synthesis of 1-(6-Hydroxy-4-methoxybenzofuran-5-yl)-3-((un)substituted)phenylprop-2-en-1-one (2a–e) The warmed solution of 5-acetyl-4-methoxybenzofuran-6-ol **1** (1.9 g, 10 mmol) and the appropriate aromatic aldehyde (11 mmol) in ethanol (20 mL) was treated with 30% sodium hydroxide solution (5 mL) and was left for 48 h at room temperature. The reaction mixture was diluted with ice water and acidified with acetic acid. The precipitate was filtered off, washed with water and dried. The crude product was crystallized from methanol (Chart 1).

1-(6-Hydroxy-4-methoxybenzofuran-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**2d**) Yield 85%. mp 159–160°C. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (9H, s, 3×OCH_3), 4.13 (3H, s, OCH_3), 6.82 (1H, s, H-7 benzofuran), 6.87 (2H, s, H-2′,6′ Ar), 6.88 (1H, d, J=1.8 Hz, H-3 furan), 7.48 (1H, d, J=2.4 Hz, H-2 furan), 7.76 (2H, d, J=16.9 Hz, COC<u>H</u>=C<u>H</u>), 12.70 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3442 (OH), 3100 (CH Ar), 2941, 2837 (CH aliphatic), 1660 (C=O), 1604, 1577, 1556, 1543, 1504 (C=C). MS (*m*/*z*) %: 384 (M^+) 68.83%. *Anal.* Calcd for $C_{21}H_{20}O_7$ (384.38): C, 65.62; H, 5.24. Found: 65.65; H, 5.28.

General Procedure for Synthesis of 1-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-3-((un)substituted)phenylprop-2-en-1-one (3a–e) To a solution of the appropriate propenone derivative **2a**–**e** (10 mmol) in ethanol (20 mL), morpholine hydrochloride (1.36 g, 11 mmol) and paraformaldehyde (0.6 g, 20 mmol) were added. The mixture was refluxed for 24 h. Excess solvent was removed under vacuum then cooled and water was added. The mixture was neutralized with dilute ammonia and extracted with chloroform. Chloroform extract was dried over anhydrous sodium sulfate and evaporated under vacuum. The product was crystallized from methanol (Chart 1).

3-(3,4-Dimethoxyphenyl)-1-[6-hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]prop-2-en-1-one (**3c**) Yield 60%. mp 158–160°C. ^{1}H-NMR ($CDCl_3$) δ: 2.90–3.00 (4H, m, morpholine H), 3.45–3.65 (4H, m, morpholine H), 3.94 (6H, s, 2×OCH_3), 4.11 (3H, s, OCH_3), 4.81 (2H, s, CH_2), 6.88 (1H, d, J=1.5 Hz, H-3 furan), 6.92 (1H, d, J=6.6 Hz, H-5′ Ar), 7.70 (1H, s, H-2′ Ar), 7.27 (1H, d, J=5.4 Hz, H-6′ Ar), 7.58 (1H, d, J=17.1 Hz, COC<u>H</u>=CH), 7.73 (1H, d, J=1.5 Hz, H-2 furan), 7.79 (1H, d, J=17.1 Hz, COCH=C<u>H</u>), 13.10 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3414 (OH), 3100 (CH Ar), 2920, 2850 (CH aliphatic), 1670 (C=O), 1616, 1604, 1560, 1541, 1508 (C=C). MS (*m*/*z*) %: 454 (M^++1) 10.53%. *Anal.* Calcd for $C_{25}H_{27}NO_7$ (453.48): C, 66.21; H, 6.00; N, 3.09. Found: C, 66.34; H, 6.09; N, 3.18.

1-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**3d**) Yield 70%. mp 134–136°C. ^{1}H-NMR ($CDCl_3$) δ: 3.46–3.51 (4H, m, morpholine H), 3.60–3.74 (4H, m, morpholine H), 3.92 (9H, s, 3×OCH_3), 4.11 (3H, s, OCH_3), 4.82 (2H, s, CH_2), 6.87 (2H, s, H-2′,6′ Ar), 6.88 (1H, d, J=2.4 Hz, H-3 furan), 7.52 (1H, d, J=2.4 Hz, H-2 furan), 7.74 (2H, d, J=16.7 Hz, COC<u>H</u>=C<u>H</u>), 13.04 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3400 (OH), 3040 (CH Ar), 2924, 2852 (CH aliphatic), 1670 (C=O), 1579, 1560, 1546, 1504 (C=C). MS (*m*/*z*) %: 483 (M^+) 0.35%. *Anal.* Calcd for $C_{26}H_{29}NO_8$ (483.51): C, 64.59; H, 6.05; N, 2.90. Found: C, 64.61; H, 6.11; N, 2.91.

3-(4-Hydroxy-3-methoxyphenyl)-1-[6-hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]prop-2-en-1-one (**3e**) Yield 62%. mp 117–118°C. ^{1}H-NMR ($CDCl_3$) δ: 2.64–2.68 (4H, m, morpholine H), 2.71–2.77 (4H, m, morpholine H), 3.49 (3H, s, OCH_3), 4.18 (3H, s, OCH_3), 4.32 (2H, s, CH_2), 6.72 (1H, s, H-2′ Ar), 6.87 (2H, d, J=9.4 Hz, H-5′,6′ Ar), 6.89 (1H, d, J=2.4 Hz, H-3 furan), 7.43 (2H, d, J=16.9 Hz, COC<u>H</u>=C<u>H</u>), 7.44 (1H, d, J=2.4 Hz, H-2 furan), 13.11 (2H, s, 2×OH exch. D_2O). IR (KBr) cm^{-1}: 3446 (OH), 3040 (CH Ar), 2924, 2852 (CH aliphatic), 1670 (C=O), 1612, 1585, 1548 (C=C). MS (*m*/*z*)

%: 442 (M^++3) 8.52%. *Anal.* Calcd for $C_{24}H_{25}NO_7$ (439.46): C, 65.59; H, 5.73; N, 3.19. Found: C, 65.63; H, 5.78; N, 3.28.

General Procedure for Synthesis of 4-Methoxy-7-(morpholin-4-ylmethyl)-5-[5-((un)substituted)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (4a–e) Hydrazine hydrate 98% (0.55 g, 0.55 mL, 11 mmol) was added to a solution of the appropriate Mannich base compound **3a**–**e** (10 mmol) in ethanol (20 mL) and the reaction mixture was refluxed for 6 h. The solvent was concentrated under reduced pressure and the residue was crystallized from methanol (Chart 1).

5-[5-(3,4-Dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (**4c**) Yield 64%. mp 145–148°C. ^{1}H-NMR ($CDCl_3$) δ: 2.88–3.00 (4H, m, morpholine H), 3.21–3.49 (4H, m, morpholine H), 3.64 (1H, dd, J=14.1, 7.5 Hz, CH_2 pyrazoline), 3.93 (6H, s, 2×OCH_3), 4.02 (3H, s, OCH_3), 4.09 (2H, s, CH_2), 4.16 (1H, dd, J=14.1, 7.8 Hz, CH_2 pyrazoline), 4.85 (1H, t, CH pyrazoline), 6.76 (1H, s, H-2′ Ar), 6.84 (1H, d, J=2.4 Hz, H-3 furan), 6.95 (1H, d, J=9.4 Hz, H-5′ Ar), 7.49 (1H, d, J=9.3 Hz, H-6′ Ar), 7.80 (1H, d, J=2.4 Hz, H-2 furan), 11.75 (1H, s, NH, exch. D_2O), 13.00 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3400 (OH), 3323 (NH), 3040 (CH Ar), 2922, 2850 (CH aliphatic), 1620, 1516 (NH, C=C). MS (*m*/*z*) %: 465 (M^+−2) 2.53%. *Anal.* Calcd for $C_{25}H_{29}N_3O_6$ (467.51): C, 64.23; H, 6.25; N, 8.99. Found: C, 64.37; H, 6.22; N, 9.17.

4-Methoxy-7-(morpholin-4-ylmethyl)-5-[5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (**4d**) Yield 70%. mp 114–117°C. ^{1}H-NMR ($CDCl_3$) δ: 2.50–2.63 (4H, m, morpholine H), 3.11–3.40 (4H, m, morpholine H), 3.82 (1H, dd, J=14.1, 7.8 Hz, CH_2 pyrazoline), 3.87 (9H, s, 3×OCH_3), 3.95 (3H, s, OCH_3), 4.03 (2H, s, CH_2), 4.33 (1H, dd, J=14.4, 8.2 Hz, CH_2 pyrazoline), 4.86 (1H, t, CH pyrazoline), 6.66 (2H, s, H-2′,6′ Ar), 6.80 (1H, d, J=2.3 Hz, H-3 furan), 7.50 (1H, d, J=2.1 Hz, H-2 furan), 10.10 (1H, s, NH, exch. D_2O), 12.40 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3446 (OH), 3260 (NH), 3100 (CH Ar), 2916, 2848 (CH aliphatic), 1618, 1593, 1560, 1540, 1508 (NH, C=C). MS (*m*/*z*) %: 499 (M^++2) 0.42%. *Anal.* Calcd for $C_{26}H_{31}N_3O_7$ (497.54): C, 62.76; H, 6.28; N, 8.45. Found: C, 62.79; H, 6.31; N, 8.52.

5-[5-(4-Hydroxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (**4e**) Yield 55%. mp 88–89°C. ^{1}H-NMR ($CDCl_3$) δ: 2.40–2.65 (4H, m, morpholine H), 3.20–3.80 (5H, m, morpholine H, CH_2 pyrazoline), 4.00 (1H, dd, J=14.1, 7.8 Hz, CH_2 pyrazoline), 4.06 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 4.20 (2H, s, CH_2), 4.85 (1H, t, CH pyrazoline), 6.75–6.90 (4H, m, H-3 furan, H-2′,5′,6′ Ar), 7.45 (1H, d, J=2.1 Hz, H-2 furan), 12.00 (1H, s, NH, exch. D_2O), 13.00 (2H, s, 2×OH, exch. D_2O). IR (KBr) cm^{-1}: 3392 (OH), 3296 (NH), 3066 (CH Ar), 2922, 2850 (CH aliphatic), 1618, 1560, 1540, 1520 (NH, C=C). MS (*m*/*z*) %: 457 (M^++4) 0.19%. *Anal.* Calcd for $C_{24}H_{27}N_3O_6$ (453.49): C, 63.56; H, 6.00; N, 9.27. Found: 63.64; H, 6.04; N, 9.39.

General Procedure for Synthesis of 5-[1-Acetyl-5-((un)substituted)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (5a–e) A mixture of the appropriate Mannich base compound **3a**–**e** (10 mmol), hydrazine hydrate 98% (0.55 g, 0.55 mL, 11 mmol) in glacial acetic acid (5 mL) was heated under reflux for 6 h. The resulting solution was cooled and poured onto ice water. The solid obtained was filtered off, washed with water and dried. The crude product was crystallized from acetic acid (Chart 1).

5-[1-Acetyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (**5a**) Yield 60%. mp 79–80°C. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, $COCH_3$), 2.20–2.50 (4H, m, morpholine H), 3.40–3.65 (4H, m, morpholine H), 3.73 (1H, dd, J=14.1, 6.9 Hz, CH_2 pyrazoline), 3.98 (3H, s, OCH_3), 4.08 (2H, s, CH_2), 4.46 (1H, dd, J=14.4, 7.2 Hz, CH_2 pyrazoline), 5.49 (1H, t, CH pyrazoline), 6.88 (1H, d, J=2.3 Hz, H-3 furan), 7.26–7.48 (3H, m, H-3′,4′,5′ Ar), 7.59 (2H, d, J=7.2 Hz, H-2′,6′ Ar), 8.08 (1H, d, J=2.2 Hz, H-2 furan), 12.70 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3417 (OH), 3061 (CH Ar), 2926, 2850 (CH aliphatic), 1666 (C=O), 1620, 1492 (C=C). MS (*m*/*z*) %: 449 (M^+) 0.11%. *Anal.* Calcd for $C_{25}H_{27}N_3O_5$ (449.50): C, 66.80; H, 6.05; N, 9.35. Found: C, 66.87; H, 6.11; N, 9.44.

5-[1-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (**5b**) Yield 64%. mp 124–125°C. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $COCH_3$), 2.34–2.43 (4H, m, morpholine H), 3.54 (1H, dd, J=18.9, 7.5 Hz, CH_2 pyrazoline), 3.71–3.85 (4H, m, morpholine H), 3.99 (3H, s, OCH_3), 4.04 (1H, dd, J=17.3, 7.9 Hz, CH_2 pyrazoline), 4.11 (3H, s, OCH_3), 4.21 (2H, s, CH_2), 5.43 (1H, t, CH pyrazoline), 6.81 (1H, d, J=2.0 Hz, H-3 furan), 6.86 (2H, d, J=11.4 Hz, H-3′,5′ Ar), 7.18 (2H, d, J=11.7 Hz, H-2′,6′ Ar), 7.46 (1H, d, J=2.1 Hz, H-2 furan), 11.80 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3431 (OH), 3066 (CH Ar), 2933, 2835 (CH aliphatic), 1664 (C=O), 1618, 1514 (C=C). MS (*m*/*z*) %: 478 (M^+−1) 0.51%. *Anal.* Calcd for $C_{26}H_{29}N_3O_6$ (479.52): C, 65.12; H, 6.10; N, 8.76. Found: C, 65.17; H, 6.17; N, 8.90.

5-[1-Acetyl-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (**5c**) Yield 67%. mp 131–132°C. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, $COCH_3$), 2.34–2.43 (4H, m, morpholine H), 3.47–3.77 (6H, m, morpholine H, CH_2 pyrazoline), 3.84 (6H, s, 2×OCH_3), 3.97 (3H, s, OCH_3), 4.21 (2H, s, CH_2), 5.41 (1H, t, CH pyrazoline), 6.78–6.97 (4H, m, H-3 furan, H-2′,5′,6′ Ar), 7.48 (1H, d, J=2.1 Hz, H-2 furan), 11.73 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3423 (OH), 3072 (CH Ar), 2924, 2850 (CH aliphatic), 1662 (C=O), 1620, 1544, 1517 (C=C). MS (*m*/*z*) %: 508 (M^+−1) 1.14%. *Anal.* Calcd for $C_{27}H_{31}N_3O_7$ (509.55): C, 63.64; H, 6.13; N, 8.25. Found: C, 63.70; H, 6.18; N, 8.38.

5-[1-Acetyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-6-ol (**5d**) Yield 70%. mp 116–117°C. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $COCH_3$), 2.30–2.56 (4H, m, morpholine H), 3.81 (9H, s, 3×OCH_3), 3.83–3.89 (6H, m, morpholine H, CH_2 pyrazoline), 3.90 (3H, s, OCH_3), 4.10 (2H, s, CH_2), 5.40 (1H, t, CH pyrazoline), 6.45 (2H, s, H-2′,6′ Ar), 6.86 (1H, d, J=2.4 Hz, H-3 furan), 7.45 (1H, d, J=2.4 Hz, H-2 furan), 11.70 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3421 (OH), 3066 (CH Ar), 2935, 2839 (CH aliphatic), 1660 (C=O), 1618, 1593, 1543, 1508 (C=C). MS (*m*/*z*) %: 539 (M^+) 0.88%. *Anal.* Calcd for $C_{28}H_{33}N_3O_8$ (539.58): C, 62.33; H, 6.16; N, 7.79. Found: C, 62.41; H, 6.13; N, 7.88.

5-[1-Acetyl-5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-7-(morpholin-4-ylmethyl)-benzofuran-6-ol (**5e**) Yield 55%. mp 101–104°C. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s, $COCH_3$), 2.71–2.78 (4H, m, morpholine H), 3.80–4.18 (6H, m, morpholine H, CH_2 pyrazoline), 4.19

(3H, s, OCH_3), 4.25 (3H, s, OCH_3), 4.28 (2H, s, CH_2), 5.40 (1H, t, CH pyrazoline), 6.76 (1H, s, H-2′ Ar), 6.88 (2H, d, J=9.9 Hz, H-5′,6′ Ar), 6.92 (1H, d, J=2.4 Hz, H-3 furan), 7.48 (1H, d, J=2.4 Hz, H-2 furan), 13.15 (1H, s, OH, exch. D_2O), 13.26 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3400 (OH), 3080 (CH Ar), 2924, 2850 (CH aliphatic), 1680 (C=O), 1620, 1589, 1548, 1517 (C=C). MS (*m*/*z*) %: 493 (M^+−2) 1.82%. *Anal.* Calcd for $C_{26}H_{29}N_3O_7$ (495.52): C, 63.02; H, 5.90; N, 8.48. Found: C, 63.16; H, 5.96; N, 8.63.

General Procedure for Synthesis of 3-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-5-((un)-substituted)phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (or Carbothioamide) (6a–j) A mixture of the appropriate Mannich base compound **3a**–**e** (10 mmol), semicarbazide or thiosemicarbazide (10 mmol) in ethanol (20 mL) in presence of few drops glacial acetic acid was heated under reflux for 8 h. The solvent was concentrated under reduced pressure and the residue was crystallized from methanol (Chart 1).

3-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**6a**) Yield 60%. mp 176–178°C. ^{1}H-NMR ($CDCl_3$) δ: 2.80–3.20 (4H, m, morpholine H), 3.60–4.00 (6H, m, morpholine H, CH_2 pyrazoline), 4.03 (3H, s, OCH_3), 4.16 (2H, s, CH_2), 4.50 (2H, s, NH_2, exch. D_2O), 5.10 (1H, t, CH pyrazoline), 6.95 (1H, d, J=2.4 Hz, H-3 furan), 7.43–7.64 (3H, m, H-3′,4′,5′ Ar), 7.64 (2H, d, J=7.8 Hz, H-2′,6′ Ar), 7.86 (1H, d, J=2.4 Hz, H-2 furan), 12.80 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3462 (OH), 3388, 3342 (NH_2), 3059 (CH Ar), 2924, 2852 (CH aliphatic), 1685 (C=O), 1618, 1570, 1543 (NH, C=C). MS (*m*/*z*) %: 449 (M^+−1) 6.16%. *Anal.* Calcd for $C_{24}H_{26}N_4O_5$ (450.49): C, 63.99; H, 5.82; N, 12.44. Found: C, 64.03; H, 5.89; N, 12.53.

3-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl)]-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**6b**) Yield 60%. mp 164–166°C. ^{1}H-NMR ($CDCl_3$) δ: 2.80–3.00 (4H, m, morpholine H), 3.47 (1H, dd, J=18.9, 5.4 Hz, CH_2 pyrazoline), 3.71–3.82 (4H, m, morpholine H), 3.84 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.11 (1H, dd, J=17.7, 4.8 Hz, CH_2 pyrazoline), 4.18 (2H, s, CH_2), 4.54 (2H, s, NH_2, exch. D_2O), 5.40 (1H, t, CH pyrazoline), 6.43 (1H, d, J=2.2 Hz, H-3 furan), 6.80–6.94 (2H, m, H-3′,5′ Ar), 7.31–7.62 (2H, m, H-2′,6′ Ar), 7.83 (1H, d, J=2.2 Hz, H-2 furan), 13.00 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3462 (OH), 3340, 3219 (NH_2), 3032 (CH Ar), 2924, 2852 (CH aliphatic), 1681 (C=O), 1620, 1604, 1583, 1543, 1512 (NH, C=C). MS (*m*/*z*) %: 483 (M^++3) 1.45%. *Anal.* Calcd for $C_{25}H_{28}N_4O_6$ (480.51): C, 62.49; H, 5.87; N, 11.66. Found: C, 62.54; H, 5.94; N, 11.72.

5-(3,4-Dimethoxyphenyl)-3-[6-hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**6c**) Yield 66%. mp 206–208°C. ^{1}H-NMR ($CDCl_3$) δ: 2.45–2.65 (4H, m, morpholine H), 3.50–3.85 (6H, m, morpholine H, CH_2 pyrazoline), 3.90 (6H, s, 2×OCH_3), 3.95 (3H, s, OCH_3), 4.04 (2H, s, CH_2), 4.40 (2H, br s, NH_2, exch. D_2O), 5.17 (1H, t, CH pyrazoline), 6.93–7.15 (4H, m, H-3 furan, H-2′,5′,6′ Ar), 7.60 (1H, d, J=2.0 Hz, H-2 furan), 12.20 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3470 (OH), 3380, 3340 (NH_2), 3100 (CH Ar), 2924, 2852 (CH aliphatic), 1690 (C=O), 1620, 1600, 1590, 1560, 1514 (NH, C=C). MS (*m*/*z*) %: 510 (M^+) 0.01%. *Anal.* Calcd for $C_{26}H_{30}N_4O_7$ (510.54): C, 61.17; H, 5.92; N, 10.97. Found: C, 61.29; H, 5.97; N, 11.09.

3-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**6d**) Yield 72%. mp 197–199°C. ^{1}H-NMR ($CDCl_3$) δ: 2.54–2.80 (4H, m, morpholine H), 3.74–3.86 (6H, m, morpholine H, CH_2 pyrazoline), 3.90 (9H, s, 3×OCH_3), 3.93 (3H, s, OCH_3), 4.05 (2H, s, CH_2), 4.30 (2H, s, NH_2, exch. D_2O), 4.60 (1H, t, CH pyrazoline), 6.88 (1H, d, J=2.4 Hz, H-3 furan), 6.94 (2H, s, H-2′,6′ Ar), 7.75 (1H, d, J=2.2 Hz, H-2 furan), 13.25 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3462 (OH), 3392, 3365 (NH_2), 3060 (CH Ar), 2926, 2852 (CH aliphatic), 1683 (C=O), 1616, 1593, 1581,1544, 1506 (NH, C=C). MS (*m*/*z*) %: 541 (M^++1) 0.03%. *Anal.* Calcd for $C_{27}H_{32}N_4O_8$ (540.56): C, 59.99; H, 5.97; N, 10.36. Found: C, 60.11; H, 6.04; N, 10.43.

5-(4-Hydroxy-3-methoxyphenyl)-3-[6-hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**6e**) Yield 55%. mp 90–93°C. ^{1}H-NMR ($CDCl_3$) δ: 2.67–2.74 (4H, m, morpholine H), 3.75–3.84 (6H, m, morpholine H, CH_2 pyrazoline), 4.11 (3H, s, OCH_3), 4.20 (2H, s, NH_2, exch. D_2O), 4.22 (3H, s, OCH_3), 4.23 (2H, s, CH_2), 4.45 (1H, t, CH pyrazoline), 6.79 (1H, s, H-2′ Ar), 6.90 (1H, d, J=2.4 Hz, H-3 furan), 6.94 (2H, d, J=9.4 Hz, H-5′,6′ Ar), 7.45 (1H, d, J=2.4 Hz, H-2 furan), 13.12 (2H, s, 2×OH, exch. D_2O). IR (KBr) cm^{-1}: 3433 (OH), 3311, 3253 (NH_2), 3068 (CH Ar), 2918, 2848 (CH aliphatic), 1685 (C=O), 1620, 1585, 1560 (NH, C=C). MS (*m*/*z*) %: 497 (M^++1) 0.23%. *Anal.* Calcd for $C_{25}H_{28}N_4O_7$ (496.51): C, 60.48; H, 5.68; N, 11.28. Found: C, 60.53; H, 5.73; N, 11.49.

3-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**6f**) Yield 65%. mp 150–152°C. ^{1}H-NMR ($CDCl_3$) δ: 2.66–2.80 (4H, m, morpholine H), 3.50 (1H, dd, J=12.0, 4.2 Hz, CH_2 pyrazoline), 3.75–3.86 (4H, m, morpholine H), 4.06 (3H, s, OCH_3), 4.07 (2H, s, CH_2), 4.17 (1H, dd, J=12.0, 3.9 Hz, CH_2 pyrazoline), 4.60 (2H, s, NH_2, exch. D_2O), 5.45 (1H, t, CH pyrazoline), 6.55 (1H, d, J=2.4 Hz, H-3 furan), 6.80–7.20 (3H, m, H-3′,4′,5′ Ar), 7.40–7.65 (2H, m, H-2′,6′ Ar), 7.85 (1H, d, J=2.4 Hz, H-2 furan), 12.80 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3421 (OH), 3327, 3253 (NH_2), 3032 (CH Ar), 2926, 2854 (CH aliphatic), 1620, 1597, 1560, 1541 (NH, C=C), 1278 (C=S). MS (*m*/*z*) %: 466 (M^+) 1.07%. *Anal.* Calcd for $C_{24}H_{26}N_4O_4S$ (466.55): C, 61.78; H, 5.62; N, 12.01. Found: C, 61.82; H, 5.67; N, 12.08.

3-[6-Hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**6g**) Yield 61%. mp 105–107°C. ^{1}H-NMR ($CDCl_3$) δ: 2.60–2.95 (4H, m, morpholine H), 3.40–3.60 (4H, m, morpholine H), 3.76 (1H, dd, J=19.8, 7.5 Hz, CH_2 pyrazoline), 3.87 (3H, s, OCH_3), 4.07 (1H, dd, J=20.1, 7.9 Hz, CH_2 pyrazoline), 4.14 (3H, s, OCH_3), 4.26 (2H, s, CH_2), 4.60 (1H, t, CH pyrazoline), 4.65 (2H, s, NH_2, exch. D_2O), 6.82 (1H, d, J=2.2 Hz, H-3 furan), 6.95 (2H, d, J=8.1 Hz, H-3′,5′ Ar), 7.48 (2H, d, J=8.2 Hz, H-2′,6′ Ar), 7.82 (1H, d, J=2.2 Hz, H-2 furan), 13.80 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3421 (OH), 3340, 3280 (NH_2), 3020 (CH Ar), 2916, 2848 (CH aliphatic), 1620, 1602, 1560, 1540, 1510 (NH, C=C), 1249 (C=S). MS (*m*/*z*) %: 498 (M^++2) 0.69%. *Anal.* Calcd for $C_{25}H_{28}N_4O_5S$ (496.58): C, 60.47; H, 5.68; N, 11.28. Found: C, 60.51; H, 5.74; N, 11.34.

5-(3,4-Dimethoxyphenyl)-3-[6-hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-4,5-dihydro-1*H*-

pyrazole-1-carbothioamide (**6h**) Yield 68%. mp 135–138°C. ^{1}H-NMR ($CDCl_3$) δ: 2.69–2.96 (4H, m, morpholine H), 3.42–3.57 (4H, m, morpholine H), 3.65 (1H, dd, J=13.5, 7.2 Hz, CH_2 pyrazoline), 3.88 (3H, s, OCH_3), 3.95 (6H, s, 2×OCH_3), 4.05 (1H, dd, J=15.3, 7.2 Hz, CH_2 pyrazoline), 4.11 (2H, s, CH_2), 4.61 (2H, s, NH_2, exch. D_2O), 4.82 (1H, t, CH pyrazoline), 6.80 (1H, d, J=2.0 Hz, H-3 furan), 6.92 (1H, d, J=7.8 Hz, H-5′ Ar), 7.16 (1H, s, H-2′ Ar), 7.68 (1H, d, J=7.8 Hz, H-6′ Ar), 7.85 (1H, d, J=2.0 Hz, H-2 furan), 13.14 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3423 (OH), 3315, 3250 (NH_2), 3040 (CH Ar), 2926, 2852 (CH aliphatic), 1618, 1598, 1544, 1512 (NH, C=C), 1263 (C=S). MS (*m*/*z*) %: 526 (M^+) 0.15%. *Anal.* Calcd for $C_{26}H_{30}N_4O_6S$ (526.60): C, 59.30; H, 5.74; N, 10.64. Found: C, 59.38; H, 5.78; N, 10.78.

3-[6-Hydroxy-4-methoxy-7-(Morpholin-4-ylmethyl)-benzofuran-5-yl]-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**6i**) Yield 68%. mp 130–132°C. ^{1}H-NMR ($CDCl_3$) δ: 2.60–3.00 (4H, m, morpholine H), 3.60–3.80 (4H, m, morpholine H), 3.78 (3H, s, OCH_3), 3.92 (9H, s, 3×OCH_3), 4.03 (1H, dd, J=15.9, 9.3, Hz, CH_2 pyrazoline), 4.12 (2H, s, CH_2), 4.16 (1H, dd, J=16.2, 9.6 Hz, CH_2 pyrazoline), 4.30 (2H, s, NH_2, exch. D_2O), 4.80 (1H, t, CH pyrazoline), 6.60 (1H, d, J=2.2 Hz, H-3 furan), 6.88 (2H, s, H-2′,6′ Ar), 7.80 (1H, d, J=2.4 Hz, H-2 furan), 13.25 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3421 (OH), 3336, 3307 (NH_2), 3080 (CH Ar), 2916, 2848 (CH aliphatic), 1620, 1593, 1581, 1558, 1541, 1506 (NH, C=C), 1284 (C=S). MS (*m*/*z*) %: 558 (M^++2) 21.13%. *Anal.* Calcd for $C_{27}H_{32}N_4O_7S$ (556.63): C, 58.26; H, 5.79; N, 10.07. Found: C, 58.34; H, 5.83; N, 10.19.

5-(4-Hydroxy-3-methoxyphenyl)-3-[6-hydroxy-4-methoxy-7-(morpholin-4-ylmethyl)benzofuran-5-yl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**6j**) Yield 60%. mp 110–113°C. ^{1}H-NMR ($CDCl_3$) δ: 2.65–2.78 (4H, m, morpholine H), 4.15–4.21 (6H, m, morpholine H, CH_2 pyrazoline), 4.22 (6H, s, 2×OCH_3), 4.30 (2H, s, CH_2), 4.40 (2H, s, NH_2, exch. D_2O), 4.80 (1H, t, CH pyrazoline), 6.72 (1H, d, J=2.4 Hz, H-3 furan), 6.73 (1H, s, H-2′ Ar), 6.89 (2H, d, J=9.4 Hz, H-5′,6′ Ar), 7.45 (1H, d, J=2.4 Hz, H-2 furan), 13.11 (2H, s, 2×OH, exch. D_2O). IR (KBr) cm^{-1}: 3442 (OH), 3151, 3124 (NH_2), 3070 (CH Ar), 2920, 2850 (CH aliphatic), 1620, 1612, 1585, 1545 (NH, C=C), 1263 (C=S). MS (*m*/*z*) %: 514 (M^++2) 19.51%. *Anal.* Calcd for $C_{25}H_{28}N_4O_6S$ (512.58): C, 58.58; H, 5.51; N, 10.93. Found: C, 58.67; H, 5.48; N, 11.18.

General Procedure for Synthesis of 4-Methoxy-5-[5-((un)-substituted)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (7a–e) Hydrazine hydrate 98% (0.55 g, 0.55 mL, 11 mmol) was added to a solution of the appropriate propenone derivative **2a–e** (10 mmol) in ethanol (20 mL) and the reaction mixture was refluxed for 3 h. The solvent was concentrated under reduced pressure and the residue was crystallized from methanol (Chart 2).

5-[5-(3,4-Dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxybenzofuran-6-ol (**7c**) Yield 65%; mp 141–142°C. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (1H, dd, J=17.4, 9.6 Hz, CH_2 pyrazoline), 3.77 (1H, dd, J=17.4, 9.9 Hz, CH_2 pyrazoline), 3.89 (6H, s, 2×OCH_3), 4.03 (3H, s, OCH_3), 4.76 (1H, t, CH pyrazoline), 6.81 (1H, s, H-7 benzofuran), 6.82 (1H, d, J=2.1 Hz, H-3 furan), 6.86 (1H, s, H-2′ Ar), 6.93 (1H, d, J=10.2 Hz, H-5′ Ar), 6.98 (1H, d, J=9.9 Hz, H-6′ Ar), 7.45 (1H, d, J=2.4 Hz, H-2 furan), 11.60 (1H, s, NH, exch. D_2O), 11.80 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3440 (OH), 3308 (NH), 3100 (CH Ar), 2947, 2848 (CH aliphatic), 1606, 1575, 1540, 1508 (NH, C=C). MS (*m*/*z*) %: 369 (M^++1) 100%. *Anal.* Calcd for $C_{20}H_{20}N_2O_5$ (368.38): C, 65.21; H, 5.47; N, 7.60. Found: C, 65.29; H, 5.51; N, 7.76.

4-Methoxy-5-[5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (**7d**) Yield 72%. mp 154–156°C. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (1H, dd, J=17.1, 9.3 Hz, CH_2 pyrazoline), 3.81 (1H, dd, J=15.3, 9.3 Hz, CH_2 pyrazoline), 3.90 (9H, s, 3×OCH_3), 4.04 (3H, s, OCH_3), 4.80 (1H, t, CH pyrazoline), 6.65 (2H, s, H-2′,6′ Ar), 6.81 (1H, d, J=2.1 Hz, H-3 furan), 6.86 (1H, s, H-7 benzofuran), 7.43 (1H, d, J=2.1 Hz, H-2 furan), 11.60 (1H, s, NH, exch. D_2O), 12.80 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3431 (OH), 3323 (NH), 3072 (CH Ar), 2939, 2831 (CH aliphatic), 1600, 1560, 1543, 1508 (NH, C=C). MS (*m*/*z*) %: 398 (M^+) 100%. *Anal.* Calcd for $C_{21}H_{22}N_2O_6$ (398.41): C, 63.31; H, 5.57; N, 7.03. Found: C, 63.37; H, 5.61; N, 7.17.

5-[5-(4-Hydroxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxy-benzofuran-6-ol (**7e**) Yield 62%; mp 166–168°C. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (1H, dd, J=15.6, 8.6 Hz, CH_2 pyrazoline), 3.75 (1H, dd, J=15.8, 8.6 Hz, CH_2 pyrazoline), 4.12 (6H, s, 2×OCH_3), 4.38 (1H, t, CH pyrazoline), 6.80 (1H, s, H-7 benzofuran), 6.84 (2H, d, J=7.7 Hz, H-5′,6′ Ar), 6.87 (1H, d, J=2.1 Hz, H-3 furan), 7.00 (1H, s, H-2′ Ar), 7.46 (1H, d, J=2.1 Hz, H-2 furan), 11.20 (1H, s, NH, exch. D_2O), 13.20 (2H, s, 2×OH, exch. D_2O). IR (KBr) cm^{-1}: 3446 (OH), 3396 (NH), 3000 (CH Ar), 2918, 2848 (CH aliphatic), 1622, 1591, 1558, 1544 (NH, C=C). MS (*m*/*z*) %: 355 (M^++1) 5.05%. *Anal.* Calcd for $C_{19}H_{18}N_2O_5$ (354.36): C, 64.40; H, 5.12; N, 7.91. Found: C, 64.47; H, 5.15; N, 7.98.

General Procedure for Synthesis of 4-Methoxy-5-[1-(morpholin-4-ylmethyl)-5-((un)substituted)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (8a–e) To a solution of the appropriate compound **7a–e** (10 mmol) in ethanol (20 mL), morpholine hydrochloride (1.36 g, 11 mmol) and paraformaldehyde (0.6 g, 20 mmol) were added. The mixture was refluxed for 24 h. Excess solvent was removed under vacuum then cooled and water was added. The mixture was neutralized with dilute ammonia and extracted with chloroform. Chloroform extract was dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified using preparative thin layer chromatography (TLC) (Chart 2).

Preparative TLC TLC was prepared by mixing the adsorbent, silica gel, with a small amount of inert binder, calcium sulfate (gypsum) and water. This mixture is spread as thick slurry on an unreactive carrier sheet, glass (20 cm×20 cm). The resultant plate was dried and activated by heating in an oven for thirty minutes at 110°C.

The compounds to be separated (about 0.5 g dissolved in chloroform) were applied to the plate as a thin even layer horizontally, 2 cm far from the bottom. When developed with the solvent (chloroform/methanol 9 : 1), the compounds separated in horizontal bands with yellow color (λ_{max} 366, 254 nm by UV Vilber Lourmat 77202 were used to determine the compound bands). The lower band (R_f is 0.16–0.32) and the upper band (R_f is 0.82–0.95) were scrapped of the baking material. The baking material was extracted with chloroform and filtered to give the isolated compound upon evaporating solvent. Lower bands yielded compounds **4a–e** (with yield 60–70%) while upper bands yielded compounds **8a–e** (with yield 30–40%).

4-Methoxy-5-[1-(morpholin-4-ylmethyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (**8a**) Yield 32%. mp 157–159°C. ^{1}H-NMR ($CDCl_3$) δ: 3.20–3.44 (4H, m, morpholine H), 3.69–3.74 (4H, m, morpholine H), 3.90 (1H, dd, J=14.7, 6.3 Hz, CH_2 pyrazoline), 3.98 (3H, s, OCH_3), 4.09 (2H, s, CH_2), 4.42 (1H, dd, J=15.0, 6.6 Hz, CH_2 pyrazoline), 5.43 (1H, t, CH pyrazoline), 6.74 (1H, d, J=2.1 Hz, H-3 furan), 6.79 (1H, s, H-7 benzofuran), 7.29–7.55 (6H, m, H-2 furan, H-2′,3′,4′,5′,6′ Ar), 11.60 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3440 (OH), 3059 (CH Ar), 2941, 2841 (CH aliphatic), 1622, 1558, 1541 (C=C). MS (*m*/*z*) %: 409 (M^++2) 9.47%. *Anal.* Calcd for $C_{23}H_{25}N_3O_4$ (407.46): C, 67.80; H, 6.18; N, 10.31. Found: C, 67.92; H, 6.22; N, 10.42.

4-Methoxy-5-[5-(4-methoxyphenyl)-1-(morpholin-4-ylmethyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (**8b**) Yield 30%. mp 145–147°C. ^{1}H-NMR ($CDCl_3$) δ: 3.20–3.35 (4H, m, morpholine H), 3.50–3.70 (4H, m, morpholine H), 3.76 (1H, dd, J=18.0, 6.6 Hz, CH_2 pyrazoline), 3.84 (3H, s, OCH_3), 3.90 (1H, dd, J=16.2, 6.6 Hz, CH_2 pyrazoline), 3.98 (3H, s, OCH_3), 4.10 (2H, s, CH_2), 5.40 (1H, t, CH pyrazoline), 6.64 (2H, d, J=6.6 Hz, H-3′,5′ Ar), 6.88 (1H, s, H-7 benzofuran), 6.85 (1H, d, J=2.1 Hz, H-3 furan), 7.30 (2H, d, J=7.1 Hz, H-2′,6′ Ar), 7.45 (1H, d, J=2.1 Hz, H-2 furan), 11.40 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3415 (OH), 3032 (CH Ar), 2931, 2835 (CH aliphatic), 1616, 1560, 1512 (C=C). MS (*m*/*z*) %: 437 (M^+) 1.10%. *Anal.* Calcd for $C_{24}H_{27}N_3O_5$ (437.49): C, 65.89; H, 6.22; N, 9.60. Found: C, 65.96; H, 6.22; N, 9.73.

5-[5-(3,4-Dimethoxyphenyl)-1-(morpholin-4-ylmethyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxybenzofuran-6-ol (**8c**) Yield 40%. mp 167–169°C. ^{1}H-NMR ($CDCl_3$) δ: 3.16–3.26 (4H, m, morpholine H), 3.49–3.72 (4H, m, morpholine H), 3.80 (1H, dd, J=20.7, 5.7 Hz, CH_2 pyrazoline), 3.89 (6H, s, 2×OCH_3), 3.93 (3H, s, OCH_3), 4.05 (1H, dd, J=20.1, 6.9 Hz, CH_2 pyrazoline), 4.21 (2H, s, CH_2), 5.70 (1H, t, CH pyrazoline), 6.73 (1H, s, H-7 benzofuran), 6.80–6.93 (3H, m, H-3 furan, H-5′,6′ Ar), 7.09 (1H, s, H-2′ Ar), 7.49 (1H, d, J=2.0 Hz, H-2 furan), 11.40 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3433 (OH), 3060 (CH Ar), 2935, 2833 (CH aliphatic), 1620, 1560, 1520, 1516 (C=C). MS (*m*/*z*) %: 467 (M^+) 0.27%. *Anal.* Calcd for $C_{25}H_{29}N_3O_6$ (467.51): C, 64.23; H, 6.25; N, 8.99. Found: C, 64.30; H, 6.29; N, 9.14.

4-Methoxy-5-[1-(morpholin-4-ylmethyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]benzofuran-6-ol (**8d**) Yield 40%. mp 175–178°C. ^{1}H-NMR ($CDCl_3$) δ: 2.85–3.00 (4H, m, morpholine H), 3.40–3.60 (4H, m, morpholine H), 3.75 (9H, s, 3×OCH_3), 3.84 (1H, dd, J=12.0, 6.9 Hz, CH_2 pyrazoline), 3.95 (3H, s, OCH_3), 4.02 (1H, dd, J=12.0, 6.3 Hz, CH_2 pyrazoline), 4.11 (2H, s, CH_2), 5.72 (1H, t, CH pyrazoline), 6.50 (1H, s, H-7 benzofuran), 6.62 (1H, d, J=2.4 Hz, H-3 furan), 6.86 (2H, s, H-2′,6′ Ar), 7.14 (1H, d, J=2.4 Hz, H-2 furan), 11.40 (1H, s, OH, exch. D_2O). IR (KBr) cm^{-1}: 3442 (OH), 3080 (CH Ar), 2937, 2837 (CH aliphatic), 1622, 1593, 1560, 1540, 1508 (C=C). MS (*m*/*z*) %: 497 (M^+) 0.23%. *Anal.* Calcd for $C_{26}H_{31}N_3O_7$ (497.54): C, 62.76; H, 6.28; N, 8.45. Found: C, 62.88; H, 6.35; N, 8.59.

5-[5-(4-Hydroxy-3-methoxyphenyl)-1-(morpholin-4-ylmethyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methoxybenzofuran-6-ol (**8e**) Yield 34%. mp 117–120°C. ^{1}H-NMR ($CDCl_3$) δ: 2.60–2.72 (4H, m, morpholine H), 3.00–3.40 (4H, m, morpholine H), 3.74 (1H, dd, J=14.7, 7.2 Hz, CH_2 pyrazoline), 3.97 (3H, s, OCH_3), 4.14 (1H, dd, J=14.4, 6.6 Hz, CH_2 pyrazoline), 4.18 (3H, s, OCH_3), 4.22 (2H, s, CH_2), 4.70 (1H, t, CH pyrazoline), 6.70 (1H, s, H-7 benzofuran), 6.80–6.90 (4H, m, H-3 furan, H-2′,5′,6′ Ar), 7.45 (1H, d, J=2.0 Hz, H-2 furan), 11.40 (2H, s, 2×OH, exch. D_2O). IR (KBr) cm^{-1}: 3408 (OH), 3060 (CH Ar), 2918, 2848 (CH aliphatic), 1618, 1560, 1541, 1510 (C=C). MS (*m*/*z*) %: 454 (M^++1) 1.63%. *Anal.* Calcd for $C_{24}H_{27}N_3O_6$ (453.49): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.69; H, 6.04 ; N, 9.33.

***In Vitro* Vasodilatation Activity Screening** The study was performed at the Pharmacology Department, National Research Centre, Dokki, Egypt, after approval from the Ethics committee of the centre and in accordance with the recommendations of the proper care and use of laboratory animals (NIH publication No. 85–23, revised 1985).

The vasodilatation activity screening procedures were carried out according to the standard reported techniques[46–48] by testing the effects of the synthesized compounds **3a**–**e**, **4a**–**e**, **5a**–**e**, **6a**–**j** and **8a**–**e** on isolated thoracic aortic rings of male Wister rats (250–350 g). Aorta was cut in 3–5 mm long rings and placed in a vertical chamber "10 mL jacketed automatic multi-chamber organ bath system (model no. ML870B6/C, Panlab, Spain)" filled with modified Krebse Henseleit solution composed of (in mM): NaCl, 118.0; KCl, 4.7; $NaHCO_3$, 25.0; $CaCl_2$, 1.8; NaH_2PO_4, 1.2; $MgSO_4$, 1.2; glucose, 11.0 and oxygenated with carbogen gas (95% O_2/5% CO_2) at 37±0.5°C. Each aorta ring was mounted between two stainless steel hooks passed through its lumen. The lower hook was fixed between two plates, while the upper one was attached to a force displacement transducer (Model no. MLT0201/ Panlab, Spain) connected to an amplifier (powerLab, AD Instruments Pty., Ltd.) which is connected to a computer. The Chart for windows (v 3.4) software was used to record and elaborate data.

Preparations were stabilized fewer than 2 g resting tension during 2 h. The lack of endothelium was confirmed by the absence of acetylcholine (1 μM) vasorelaxent action in aortic rings precontracted by noradrenalin (0.1 μM). The contractile response to norepinephrine hydrochloride (10^{-6} M) was measured before and after exposure to increasing concentrations of the tested compounds. The tested compounds as well as prazosin (as reference standard) were dissolved in dimethyl sulfoxide (DMSO) as stock solution (10 mL of 0.01 M). Control experiments were performed in the presence of DMSO alone, at the same concentrations as those used with the derivatives tested, which demonstrated that the solvent did not affect the contractile response of isolated aorta. The observed vasodilatation activity data are reported (Table 1, Fig. 2) and the potency (IC_{50}, concentration necessary for 50% reduction of maximal norepinephrine hydrochloride induced contracture) was determined by the best fit line technique.

QSAR Computational Method All the computational works were performed on Molecular Operating Environment software (MOE version 2008.10.2).[52] The structures of 30 compounds used as training set were sketched using molecular builder of MOE and each structure was subjected to energy minimization up to 0.01 kcal/mol Å using the MMFF94x force field. Optimization methods were used followed by conformational search of each energy-minimized structure. The most stable conformer of each structure was selected and saved into the database to generate the common descriptors. QuaSAR descriptor module of MOE was used to calculate descriptors for each molecule. The probability density functions used are

Gaussian. The RMSD tolerance was set to 0.5 Å. Regression analysis was performed using vasodilator IC_{50} as dependent factor and the calculated descriptors as predictable variables.

In this study, the pool of descriptors was optimized using principal components analysis (PCA). The optimization started with the reduction in the number of molecular descriptors by the determination of the highly inter-correlated descriptor pairs and only one from each pair was selected; then the descriptors with insignificant variance through the data set were also rejected. QSAR model was then constructed after ensuring reasonable correlation of vasodilator activity with the individual descriptors and minimum inter-correlation among the descriptors used in the derived model. The quality of the model was assessed using the statistical parameter r^2 and q^2.

Molecular Descriptors Log S: Log of the aqueous solubility (mol/L). This property was calculated from an atom contribution linear atom type model with $r^2=0.90$.

VSA: van der Waals surface area. A polyhedral representation was used for each atom in calculating the surface area.

E_sol: Solvation energy. In the Potential Setup panel, the term enable parameter (Solvation menu) was ignored, but the term weight is applied.

rgyr: Radius of gyration, Table 2.

Validation and Cross-Validation of the Model The log observed activities (log Obs. IC_{50}) together with the log predicted activities (log Pred. IC_{50}) for the tested compounds calculated using multi-linear regression (MLR) were listed in Table 3. All compounds showed very good results with *Z*-scores not exceeding the value of 2.5 indicating excellent predictive ability of the model.[53)]

The log observed IC_{50} were plotted against their log predicted values (calculated by MLR method) with a value of r^2 found to be 0.9074, Fig. 3.

Cross-validation statistical technique was applied to estimate the quality with regard to predictive ability of the generated model. This is the most common validation technique, where a number of modified data sets were created by deleting, in each case, one or a smaller group of objects from the data in such a way that each object is taken away once and only once. For each reduced data set, the model was calculated, and responses for the deleted objects were predicted from the model. The simplest and most general cross-validation procedure is the leave-one-out technique (LOO technique), where each object of the data set is taken away, one at a time. The log observed activities (log Obs. IC_{50}) together with the log predicted activities (log Pred. IC_{50}) for the tested compounds calculated using multi-linear regression (LOO) were listed in Table 3. Each log observed IC_{50} was plotted against its log predicted values (calculated by LOO method) with a value of q^2 found to be 0.860459, Fig. 4.

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