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SYNTHESIS OF SOME NEW ISOINDOLINE-1,3-DIONE BASED HETEROCYCLES

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Abstract – 2-(4-((4-Oxothiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-3-carbonyl)-isoindoline-1,3-dione **7** was prepared as new three–pharmacophoric–motif key intermediate. Compound **7** was incorporated in a series of manipulations including cyclocondensation reactions to afford a series of four–pharmacophoric–motif conjugates **9**, **11**, **12**, **15**, **16**, **19** and **21** in good yields. The newly synthesized compounds were characterized by IR, NMR, MS and elemental analyses.

INTRODUCTION

Merging of chemical architectures of significant pharmacophoric activities has been emerged as paradigmatic strategy in quest for developing probes of impressive therapeutic potentials, in particular against profound diseases.[1] Phthalimides, pyrazoles and thiazolidinones, also known as glitazones, are amongst the heteroaryls of pivotal rule in drug design and material science as well. Thus, the antimicrobial[2–4] and hypolipidemic[5] activities of phthalimides and *N*-substituted phthalimides were reported. TRK–130 (Naltalimide) (**Figure 1**) is a potential new therapeutic agent for overactive bladder.[6] Industrially, they are widely employed as feed stocks for manufacturing pesticides,[7] polymers[8,9] as well as plasticisers.[10]

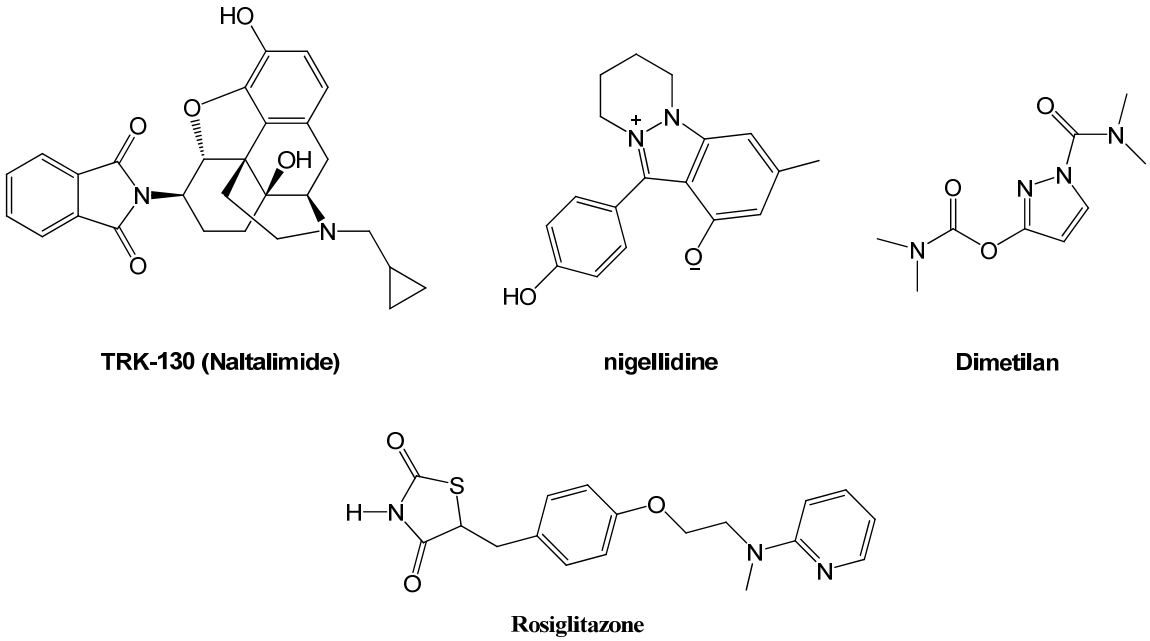


Figure 1. Representative examples of active phthalimides pyrazoles and thiazolidinones

Pyrazoles, the second heteroaryls in this introduction, exhibited numerous biological activities, including anti-diabetic, antiviral, anti-inflammatory, antimicrobial,[11,12] anticancer[13,14] and antiobesity.[15] They were explored as insecticides,[16] for example, the natural indazole alkaloid nigellidine from the seeds of *Nigella sativa*[17] and Dimetilan (**Figure 1**).[18] The later is a trade mark pyrazole containg pesticide. Pyrazoles were applied in liquid crystal developments and other material science.[19]

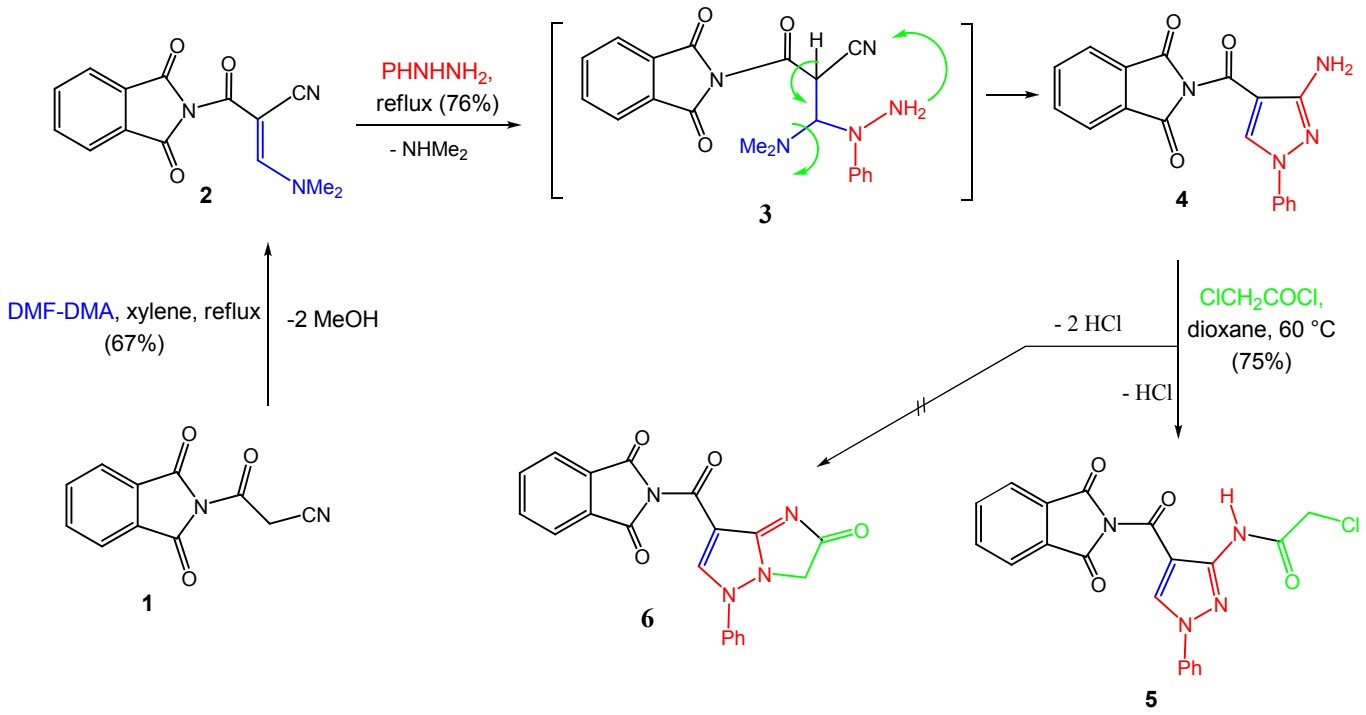
Finally, as third motif in this preface, thiazolidinones offered unique divergent pharmacological features such as antibacterial[20] including tubercular,[21] antifungal,[22] antioxidant,[23] antiproliferative,[24] analgesic, anti-inflammatory[25,26] and anticonvulsant activities. They also displayed a panel of antiviral activities including, anti–yellow fever virus (YFV),[27] anti–HIV[28] and other viral strains.[29] Thiazolidinones represent a familly of trade mark anti-diabetes mellitus *type II* theutics, for instance Rosiglitazone (**Figure 1**). The issue of pharmacological significances of thiazolidinones was reviewed[30,31] and applications of thiazolidinone dyes were reported.[32] With these precedents, we initiated a program aiming at merging of multipharmacophores in single architectures.[33–38] Herein, we describe the synthesis of **7** as key intermediate adorned with a reactive thiazolidinone tag. We were intrigued by incorporation of this reactive tag in a series of condensations and cyclocondensation manipulations. It was envisioned that, the confluence of four pharmacophors in the resulting motifs might evoke eminent pharmacological potencies.

RESULTS AND DISCUSSION

Thiazolidinone tagged intermediated **7** was prepared from **1**[38] on four steps (**Schemes 1 & 2**). Thus,

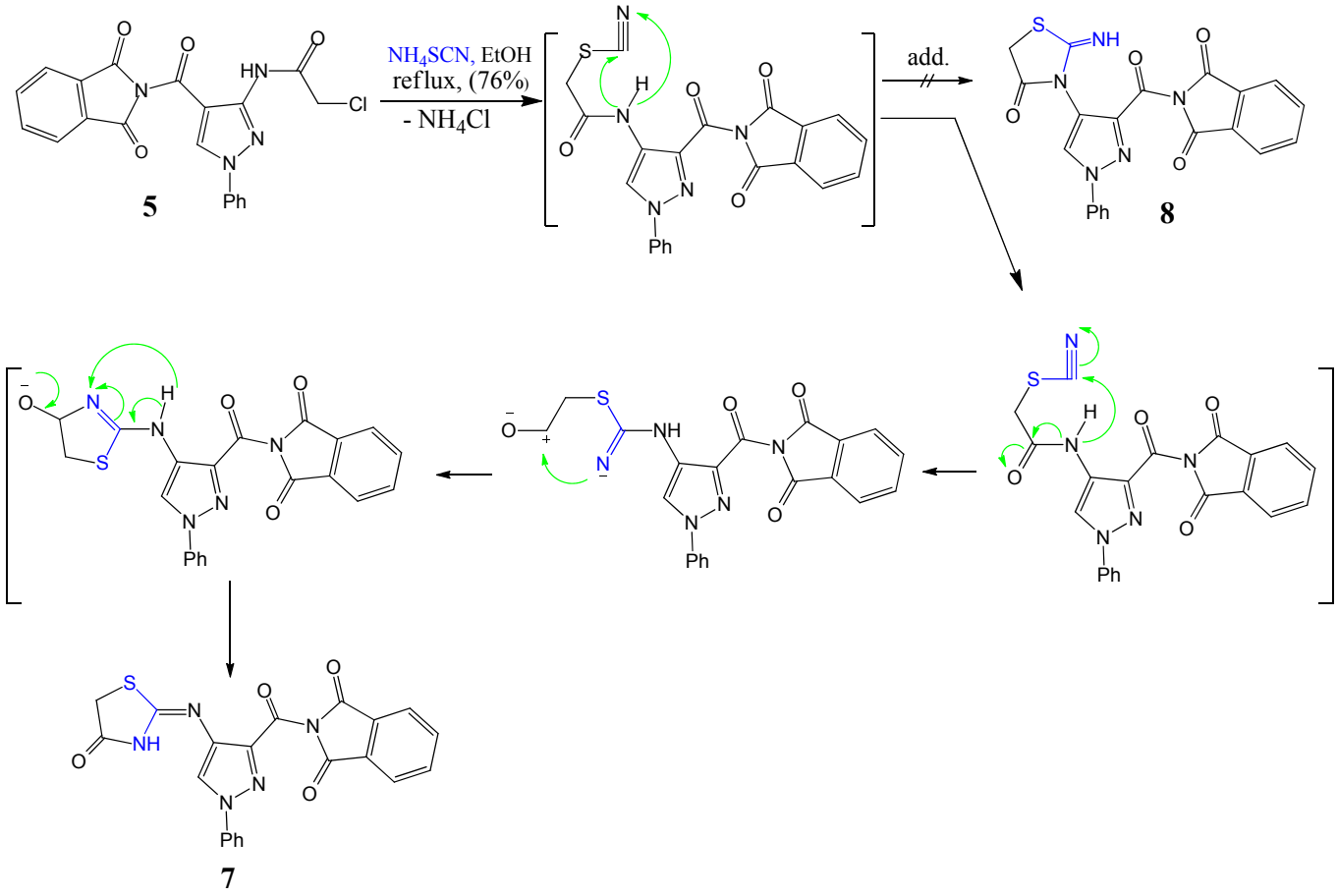
compound **1** was treated with dimethylformamide dimethyl acetal (DMF–DMA) in refluxing xylene to afford enaminonitrile **2** in 67% yield. Beside the three C=O*str* bands at ≈ 1690 and 1715 cm^{-1} and the C≡N*str* band at 2196 cm^{-1}, the NMe_2 protons (^{1}H NMR) appeared as two singlet at δ 3.27 and 3.33, the olefinic proton was observed as singlet δ 6.86 ppm. The stereochemistry of the enaminonitrile **2** was checked by the hyperchem program using the force-field MM+ method which reviled the *E*-form to be the most stable configuration. This deduction was in accordance with the reported related work.[39-41] In addition the calculated heat of formation of the *E* isomer of **2** is 26.4 kJ/ mole lower than that for the *Z* isomer, thus, the configuration *E* that is favored over the *Z*.

Cyclocondensation of **2** with $PhNHNH_2$ in refluxing EtOH afforded pyrazole derivative **4** in 76% yield. The reaction proceeded through Michael addition followed by cycloaddition of the amino group to the nitrile moiety. Compound **4** showed a band at 3405 cm^{-1} corresponding to the NH_2 *str.* with concurrent disappearance of the nitrile band and the olefinic singlet (^{1}H NMR) at δ ≈ 6.90 ppm. Its mass spectrum showed a peak at *m/z* 332, corresponding to its molecular formula $C_{18}H_{12}N_4O_3$. Subsequent chloroacetylation of **4** in warm dioxane afforded **5** in 75% yield (**Scheme 1**). The recorded mass at *m/z* 408.00 corresponding to the formula $C_{20}H_{13}ClN_4O_4$, besides the N–H*str.* band at 3208 cm^{-1} and its broad singlet (^{1}H NMR) at δ 8.87 ppm all favored formation of **5** over a pyrazoloimidazole **6** cyclocondensation pathway of this step.



Scheme 1. Synthesis of 2-chloro-*N*-(1-phenyl-1*H*-pyrazol-3-yl)acetamide drevative **5**

Compound **5** was treated by NH_4SCN in refluxing EtOH to afford **7** (**Scheme 2**) in 76% yield. A recorded *m/z* value of 431.00 can`t discriminate **7** from **8** as expected another reaction pathway. However, the observed ^{1}H NMR signal at δ 11.89 ppm for the N–H bond supported nucleophilic substitution of the chlorine atom by the thiocyanate moiety followed by intramolecular Dimroth–like rearrangement[42] over formation of imine **8**. The later one was reported in similar cases by Vicini *et al.*[43] where the imine proton appears at $\delta \approx$ 8.00 ppm (^{1}H NMR). The N–H$_{str.}$ band was observed at 3205 cm^{-1}. The latter product may be in (*Z* and/ *or E*) forms but *Z* form was ruled out based on that; The most characteristic signals of compound **7** in ^{1}H NMR spectrum belong to thiazolidinone methylene protons located at 3.83 ppm and to the exchangeable (NH) proton, which form intramolecular hydrogen bonds and can be seen in the region of 12–14 ppm for *Z* isomer. The ^{1}H NMR spectrum of compound **7** didn't display any characteristic exchangeable signals as pairs of doublets, no splitting of this signal clearly indicates there is no scalar interaction between NH and C=O. Thus, the configuration *E* that is favored over the *Z*.

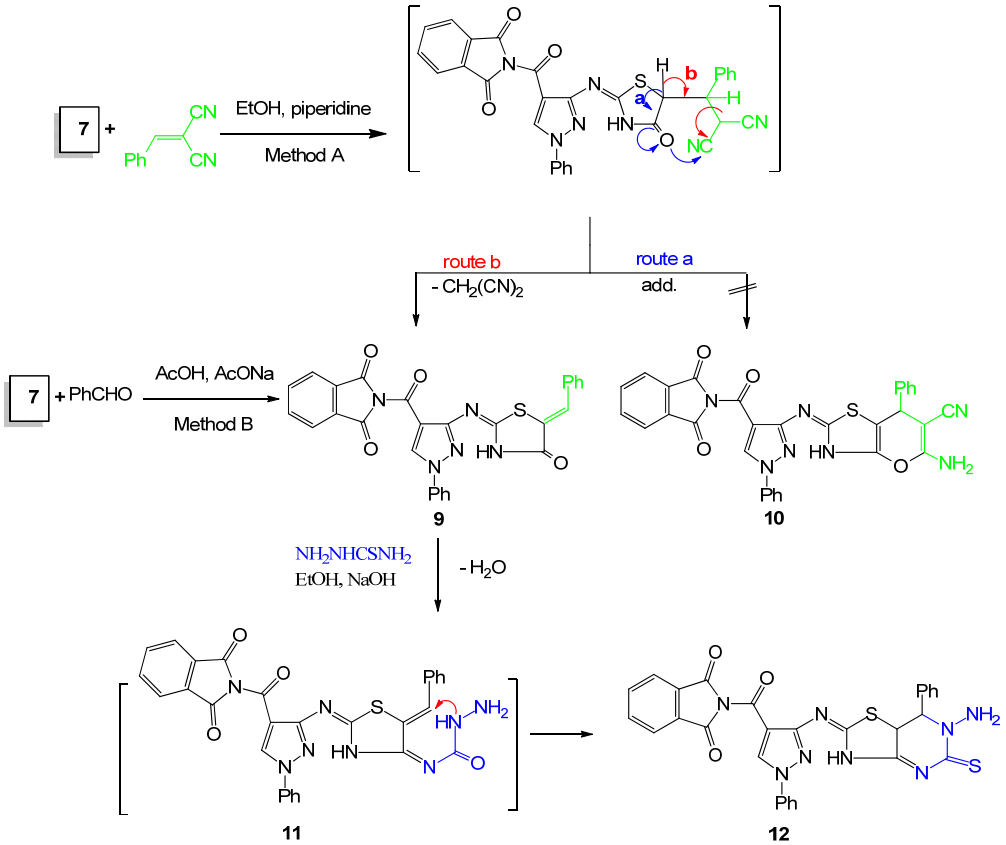


Scheme 2. Synthesis of thiazolidinone intermediate **7**

Then, compound **7** was incorporated in a set of investigations aiming at exploiting the reactivity of its thiazolidinoe tag to build up the target four–motive architectures. Thus, compound **7** was treated with

benzylidenemalononitrile containing catalytic piperidine aiming at annulation of pyranothaizole derivative **10** (**Scheme 3**). However, the *m/z* recorded at 519.00 of the isolated product ruled out this assumption and favoured splitting of malononitrile upon Michael addition affording benzylidene derivative **9** in 84% yield. For further confirmation, compound **7** was treated traditionally with benzaldehyde in glacial AcOH containing NaOAc. This digestion afforded again compound **9**, but in lower yield. The signal of the methylene protons originally observed in **7** (^{1}H NMR) at δ 3.83 ppm was disappeared, while the N–H signal was still observable at δ 10.01 ppm and its stretching band (IR) was observed at 3182 cm^{-1}. Neither the C≡N nor the NH_2 groups were observed in the IR spectra, while three C=O bands were observed at 1657, 1695 and 1701 cm^{-1} corresponding to the equivalent carbonyls of the phthalimido moiety, the exocyclic and thiazolidinone carbonyls. The olefinic proton observed as singlet at δ 7.71 ppm.

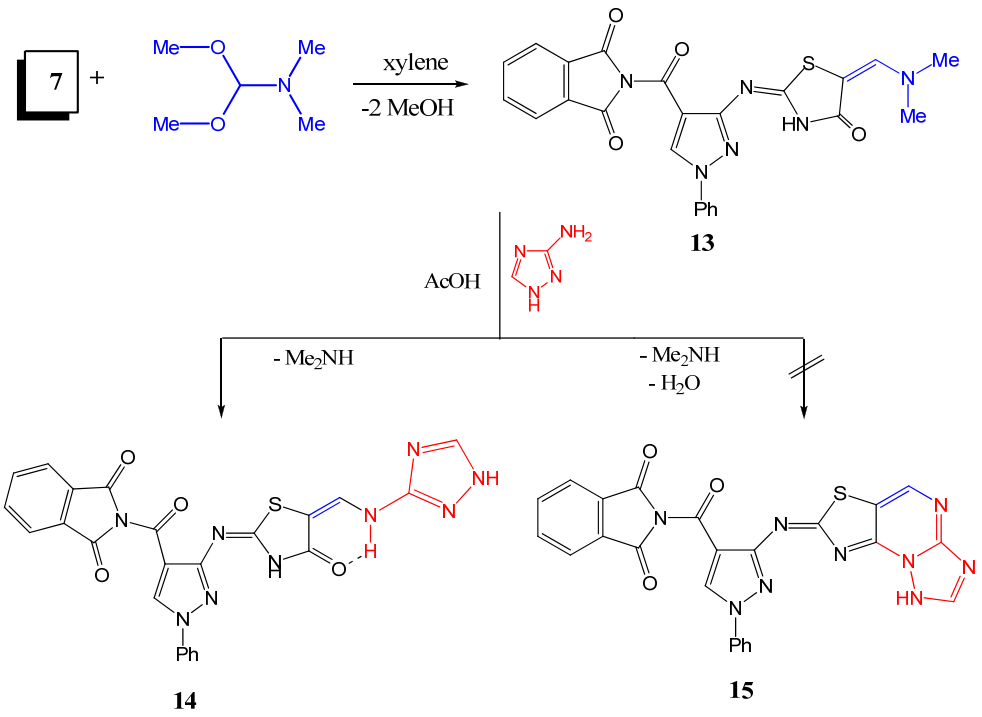
Furthermore, cyclocondensation of **9** with thiosemicarbazide proceeded smoothly in refluxing EtOH containing NaOH to afford thiazolo[4,5-*d*]pyrimidine derivative **12** in 55% yield. The mass spectrum showed a peak at *m/z* 592.00 corresponding to the molecular formula $C_{29}H_{20}N_8O_3S_2$. The IR spectrum showed strong absorption bands at 1332, 3480 cm^{-1} due to C=S and NH_2 groups, respectively, while The ^{1}H NMR spectrum displayed two broad singlets at δ 3.01 ppm and 10.01 for the NH_2 and NH groups, respectively.



Scheme 3. Synthesis of thiazolo[4,5-*d*]pyrimidine derivative **12**

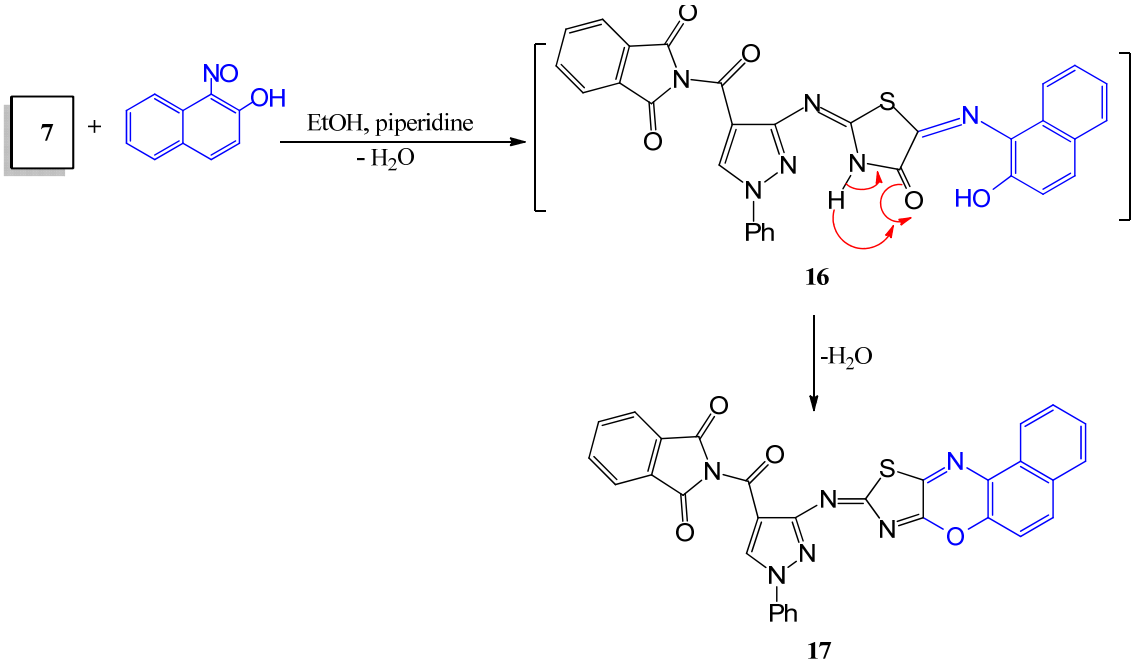
Compound **7** was converted in another investigation into the active enamine derivatives **13** in 79% yield by condensation with dimethylformamide dimethyl acetal (DMF–DMA) in refluxing xylene (**Scheme 4**). The IR spectrum of the latter product revealed the presence of N–H stretching band at 3152 cm^{-1} and three amidic C=O stretching bands at 1657, 1695 and 1701 cm^{-1}. Its mass spectrum showed the molecular ion at *m/z* 486 corresponding to its molecular formula $C_{24}H_{18}N_6O_4S$. The ^1H NMR spectrum exhibited two sharp singlets at δ 3.27 and 3.28 ppm assignable to *N,N*-dimethylamino protons, while the olefinic proton was observed as singlet at δ 6.86 ppm, besides the N–H broad singlet at δ 10.11 ppm.

Reaction of **13** with equimolar amount of 3-amino-1*H*-1,2,4-triazol (**Scheme 4**) proceeded *via* simple nucleophilic substitution to afford 2-(3-(5-(((1*H*-1,2,4-triazol-3-yl)amino)methylene)-4-oxothiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindoline-1,3-dione (**14**) in 77% yield without further cyclocondensation into triazolopyrimidine **15** as shown from the mass spectrum which gave an *m/z* peak at 525.00 corresponding to the molecular formula $C_{24}H_{15}N_9O_4S$ of **14**. The IR spectrum showed strong stretching vibration bands at 1657, 1695, 1701 and 3156–3211 cm^{-1} corresponding to the three amidic C=O and three N–H groups, respectively. The ^1H NMR spectrum showed two doublet signals at δ 6.86 (*d*, 1H, *J* 10.8 Hz, =CH) and 4.01 (*d*, 1H, *J* 10.8 Hz, =CH–NH), which support that the (triazolylamino)methylidene moiety of **14** in (*E*-form), thus, compounds **14** assigned the (*E*) configuration which is stabilized by hydrogen bonding rather than the (*Z*) configuration which could suffer from steric hindrance.



Scheme 4. Synthesis of 1,2,4-triazolo derivative **14**

Also, the 4-thiazolidinone **7** was cyclocondensed with 1-nitroso-2-naphthol in refluxing EtOH containing catalytic piperidine to afford (*E*)-2-(3-(9*H*-naphtho[1,2-*e*]thiazolo[4,5-*b*][1,4]oxazin-9-ylideneamino)-1-phenyl-1*H*-pyrazole-4-carbonyl)-isoindoline-1,3-dione (**17**) *via* the intermediate **16** which subsequently cyclized through elimination of another molecule of water as shown in **Scheme 5**. The IR spectrum of **17** showed absorption bands at 1657, 1695 and 1701 cm^{-1} attributed to three carbonyl groups and revealed the lack of that attributed to imino group. Its ^1H NMR spectrum showed the disappearance of the methylene protons and the thizolidinone N–H signals. The mass spectrum of **17** displayed an intense peak at *m/z* 568 (M^+, 45%) corresponding to the expected molecular formula $C_{31}H_{16}N_6O_4S$.

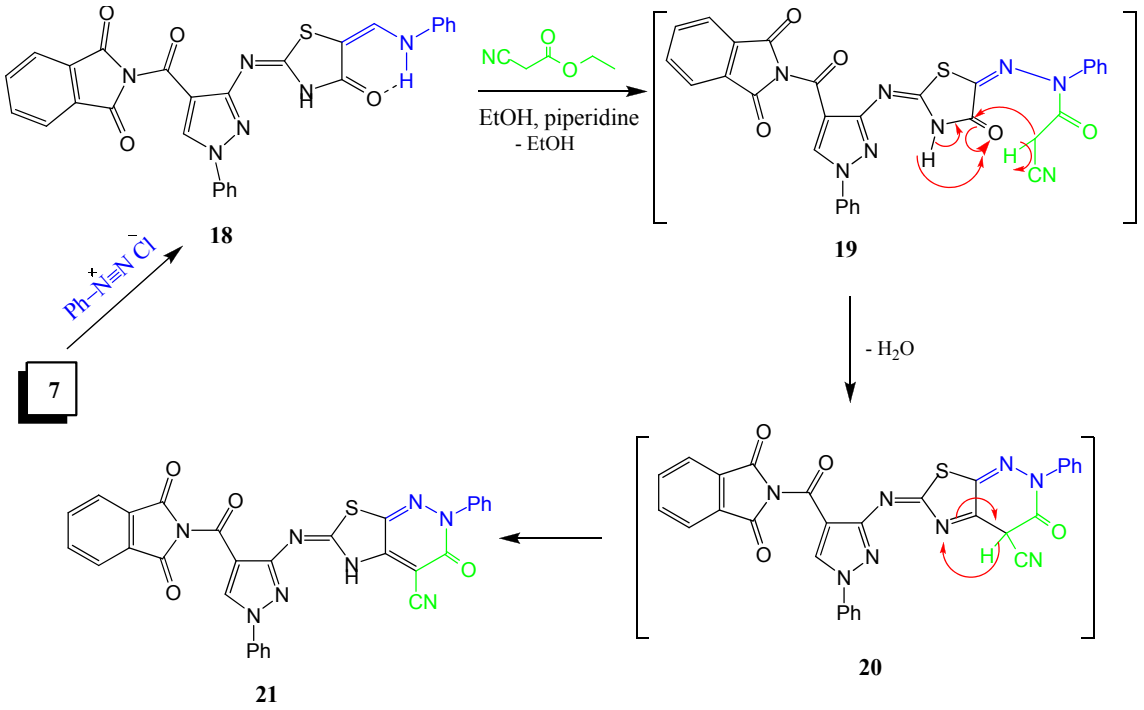


Scheme 5. Synthesis of naphtho[1,2-*e*]thiazolo[4,5-*b*][1,4]oxazine derivatives **17**

Compound **7** was coupled with benzenediazonium chloride to afford 2-(3-((*E*)-((*E*)-(4-oxo-5-(2-phenylhydrazono)thiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindo-line-1,3-dione (**18**) in good yield (**Scheme 6**). The IR spectrum of **18** revealed the presence of NH stretching absorption band at 3156–3211 cm^{-1} and three amidic C=O stretching bands at 1657, 1695 and 1701 cm^{-1}. Its mass spectrum showed a molecular ion at *m/z* 535 corresponding to its molecular formula $C_{27}H_{17}N_7O_4S$. Also, the ^1H NMR spectrum showed two broad singlets at δ 10.01 and 11.12 ppm for the 2 NH groups.

Treatment of the latter product with ethyl cyanoacetate, in boiling EtOH containing catalytic amount of piperidine afforded (*E*)-6-(4-(1,3-dioxoisoindoline-2-carbonyl)-1-phenyl-1*H*-pyrazol-3-ylimino)-3-oxo-2-phenyl-2,3,5,6-tetrahydrothiazolo[5,4-*c*]pyridazine-4-carbonitrile (**21**) *via* intermediates **19** and **20**. These intermediates were assumed to be formed through initial elimination of EtOH to form **19** followed by

cyclocondensation as shown in **Scheme 6**. The IR spectrum supported imine–enamine tautomerism as a band at 3128 cm^{-1} was still observable. This was further evidenced by its ^1H NMR broad singlet at δ 10.01 ppm without observation of any signal in the upfield region if intermediate **20** was existing. The C≡N band appeared at 2212 cm^{-1}.



Scheme 6. Synthesis of thiazolo[5,4-c]pyridazine derivative **21**

CONCLUSIONS

In summary, 2-(4-((4-oxothiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-3-carbonyl)isoindoline-1,3-dione (**7**) was prepared as new three–pharmacophoric–motif key intermediate in good yield. The reactivity of the terminal thiasolidinone tag was exploited in a series of functionallizations encompassing cyclocondensation for the modular synthesis of new four–pharmacophoric–motif probes. A panel of pharmacological investigations on these new probes is going in due course.

EXPERIMENTAL

Reagents were purchased from Sigma Aldrich and used without further purification. Reaction progress was monitored by TLC on silica gel precoated F254 Merck plates. Spots were visualized by ultraviolet irradiation. Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as potassium bromide discs using Bruker-Vector 22 FTIR

Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker WP spectrometer using DMSO–d_6 as solvent, while, TMS was used as internal standard. Mass spectra were recorded on a Hewlett Packard MS–5988 spectrometer at 70 eV. Elemental analyses were carried out at the Micro-analytical Unit, Faculty of Science, Mansoura University, Egypt.

(*E*)-3-(Dimethylamino)-2-(1,3-dioxoisoindoline-2-carbonyl)acrylonitrile (2). A mixture of 3-(1,3-dioxoisoindolin-2-yl)-3-oxopropanenitrile **1**[38] (2.14 g, 0.01 mol), and DMF–DMA (1.19 g, 0.01 mol) in dry xylene (30 mL) was refluxed for 6 h. The solvent was distilled off under reduced pressure and the residual reddish brown viscous liquid was taken in Et_2O. The resulting brown crystals were filtered off, washed thoroughly with Et_2O, dried then recrystallized from MeOH to afford **2** (67%) as brown crystals. mp 281–283 ºC; IR (KBr): ν (cm^{-1}) 1690, 1715 (3 C=O*str*), 2196 (C≡N*str*); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.27 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 6.86 (*s*, 1H, =C–H), 7.71–7.88 (m, 4H, Ar); ^{13}C NMR (75 MHz, DMSO–d_6): δ 42.3 (2 CH_3), 98.8, 114.3, 123.7, 132.2, 156.1 (6 C–Ph, C=C, C≡N), 164.2, 169.2 (3 C=O); MS (*m/z*, %): 269.0 (M^+, 50%). Anal. Calcd for $C_{14}H_{11}N_3O_3$ (269.26): C, 62.45; H, 4.12; N, 15.61%. Found: C, 62.35; H, 4.05; N, 15.49%.

2-(3-Amino-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindoline-1,3-dione (4). A mixture of **2** (0.269 g, 0.001 mol) and $PhNHNH_2$ (0.216 mL, 0.002 mole) in EtOH (20 mL) was refluxed for 4 h then left overnight at rt. The solid product so formed was filtered off, washed with EtOH, dried well, and recrystallized from (EtOH–DMF, 1:1) to afford **4** (76%) as yellow crystals. mp 122–124 ºC; IR (KBr): (cm^{-1}) 1660, 1690 (3 C=O*str.*), 3454, 3405 (NH_2 *str.*); ^{1}H NMR (300 MHz, DMSO–d_6): δ 6.51 (br. s, 2H, NH_2), 7.51–8.00 (m, 9H, Ar), 8.23 (s, 1H, H–5$_{Pyraz.}$); ^{13}C NMR (75 MHz, DMSO–d_6): 119.9, 126.2, 127.9, 129.3, 139.2, 153.3, 161.0 (12 C–Ar, 3 C–Pyraz.), 168.2, 169.2 (3 C=O); MS (*m/z,* %): 332.0 (M^+, 62%); Anal. Calcd for $C_{18}H_{12}N_4O_3$ (332.31): C, 65.06; H, 3.64; N, 16.86%. Found: C, 65.01; H, 3.45; N, 16.49%.

2-Chloro-*N*-(4-(1,3-dioxoisoindoline-2-carbonyl)-1-phenyl-1*H*-pyrazol-3-yl)acetamide (5). A mixture of chloroacetyl chloride (0.02 mol) in dry dioxane (50 mL) was added dropwise during 1 h to a well stirred solution of **4** (0.01 mol) in dry dioxane (150 mL) at 60 °C. The mixture was stirred for further 1 h, cooled then poured onto ice–cooled H_2O. The mixture was filtered and the crude was recrystallised from EtOH to afford **5** (75%) as orange crystals. mp 258–260 ºC; IR: ν (cm^{-1}) 1660, 1685, 1715 (4 C=O), 3208 (N-H*str*); ^{1}H NMR (300 MHz, DMSO–d_6): δ 4.22 (s, 2H, CH_2), 7.20–8.85 (m, 10H, 9 H–Ar, H–5$_{Pyraz.}$), 8.87 (br. s, 1H, N–H); MS: *m/z* 408.0 (M^+, 54%). Anal. Calcd for $C_{20}H_{13}ClN_4O_4$ (408.79): C, 58.76; H,

3.21; N, 13.71%. Found: C, 58.69; H, 3.14; N, 13.49%.

(*E*)-2-(4-(4-Oxothiazolidin-2-ylideneamino)-1-phenyl-1*H*-pyrazole-3-carbonyl)isoindoline-1,3-dione (7). A mixture of **5** (4.0 g, 10 mmol) and NH_4SCN (1.14 g, 15.0 mmol) in dry EtOH (30 mL) was refluxed for 6 h and allowed standing overnight. The formed precipitate was filtered off, washed with H_2O then recrystallised from EtOH to afford **7** (76%) as yellow crystals. mp 195–197 ºC; IR: ν (cm^{-1}) 1632 (C=N_{str}), 1657, 1695, 1701 (4 C=$O_{str.}$), 3205 (N-$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 3.83 (s, 1H, CH_2–Thiaz.), 7.21–7.81 (m, 10H, 9 H–Ar, H–$5_{Pyraz.}$), 11.89 (br. s, 1H, N–H); ^{13}C NMR (75 MHz, DMSO–d_6): 32.7 (CH_2–Thiaz.), 119.9, 123.7, 127.70, 132.00, 132.20, 139.90, 153.30, 158.70, 162.20, 163.00 (12 C–Ar, 3 C–Pyraz., C=N), 167.2, 169.2, 173.0 (4 C=O); MS: *m/z,* 431.0 (M^+, 35%). Anal. Calcd for $C_{21}H_{13}N_5O_4S$ (431.42): C, 58.46; H, 3.04; N, 16.23%. Found: C, 58.32; H, 3.01; N, 16.10%.

(*E*)-2-(3-((5-Benzylidene-4-oxothiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)-isoindoline-1,3-dione (9).

Method A: A mixtures of **7** (2.15 g, 5.0 mmol) and benzylidinemalononitrile (0.77 g, 5.0 mmol) in EtOH (30 mL) containing few drops of piperidine (5 drops) was stirred under reflux for 3 h. Then, the reaction mixture was cooled to rt. The solid formed was filtered, washed with hot EtOH, and recrystallized from (dioxane–DMF, 1:2) to afford **9** (84%) as yellow crystals.

Method B: A mixture of **7** (2.15 g, 5.0 mmol) and BzH (5.0 mmol) in AcOH (25 mL) containing NaOAc (10.0 mmol) was refluxed for 5 h. The reaction mixture was cooled to rt then poured onto ice–cooled H_2O. The precipitate was filtered off, washed with H_2O and the crude product was recrystallized to afford **9** (71%). mp 243–245 ºC; IR: ν (cm^{-1}) 1632 (C=N_{str}), 1657, 1695, 1701 (4 C=$O_{str.}$), 3182 (N–$H_{str.}$). ^{1}H NMR (300 MHz, DMSO–d_6): δ 7.21–7.49 (m, 15H, 14 H–Ar, H–$5_{Pyraz.}$) 7.71 (s, 1H, =C–H), 10.01 (br.s, 1H, N–H). ^{13}C NMR (75 MHz, DMSO–d_6): 116.00, 119.90, 123.70, 127.70, 132.00, 132.20, 139.90, 153.3, 158.7, 162.20 , 163.00 (18 C–Ar, 3 C–Pyraz., C=C, C=N), 167.20, 168.00, 169.20 (4 C=O),. MS: *m/z,* 519.0 (M^+, 70%); Anal. Calcd for $C_{28}H_{17}N_5O_4S$ (519.53): C, 64.73; H, 3.30; N, 13.48%. Found: C, 64.62; H, 3.11; N, 13.30%.

(*E*)-2-(3-(6-Amino-7-phenyl-5-thioxo-5,6,7,7a-tetrahydrothiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene-amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindoline-1,3-dione (12). A mixture of **9** (0.01 mol), thiosemicarbazide (0.01 mol) and NaOH (0.025 mol) in EtOH (50 mL) was heated under reflux for 8 h. The mixture was filtered while hot and the cooled filtrate was poured onto acidified ice/ water. The

precipitate formed was filtered, washed with water, dried well, and crystallized from MeOH to afford **21** (55%) as yellow crystals. mp 263–265 °C; IR (KBr): ν (cm^{-1}) 1630 (C=N_{str}), 1657, 1692, 1704 (3C=O) and 3128–3314 (NH and NH_2); ^1H NMR (300 MHz, DMSO–d_6): δ 3.01 (*s*, 2H, $NH_{2Deutr.\ Exch.}$), 4.21 (*s*, 1H, H–$5_{Pyrim.}$), 7.51–7.71 (*m*, 15H, 14 H–Ar, H–$5_{Pyraz.}$), 10.01 (*s*, 1H, N–$H_{Deutr.\ Exch.}$); MS: *m/z* 592.0 (M^+, 70%). Anal. Calcd for $C_{29}H_{20}N_8O_3S_2$ (592.65): C, 58.77; H, 3.40; N, 18.91%. Found*:* C, 58.67; H, 3.25; N, 18.84%.

2-(3-((*E*)-((*E*)-5-((dimethylamino)methylene)-4-oxothiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindoline-1,3-dione (13). A mixture of **7** (2.15 g, 5 mmol), DMF–DMA (0.6 g, 5.0 mmol) in dry xylene (30 mL) was refluxed for 6 h. The solvent was distilled off *in vacuo* and the residual orange viscous liquid was taken in Et_2O. The resulting orange crystals were filtered, washed thoroughly with Et_2O, dried then recrystallized from dioxane to afford **11** (79%) as pale orange crystals. mp 275–277 °C; IR: ν (cm^{-1}) 1632 (C=N_{str}), 1657, 1695, 1701 (4 C=$O_{str.}$), 3182 (N–$H_{str.}$). ^1H NMR (300 MHz, DMSO–d_6): δ 3.27 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 6.86 (s, 1H, =C–H), 7.21–7.49 (m, 10H, 9 H–Ar, H–$5_{Pyraz.}$), 10.11 (br. *s*, 1H, N–H). ^{13}C NMR (75 MHZ, DMSO–d_6): 42.4 (2 CH_3), 99.0, 119.90, 123.70, 127.70, 132.00, 132.20, 139.90, 153.00, 153.30, 158.70, 163.00, 162.20 (C=C, C=N, 3 C–Pyraz., 12 C–Ar), 167.2, 169.2, 168.0 (4 C=O); MS: *m/z,* 486.0 (M^+, 55%). Anal. Calcd for $C_{24}H_{18}N_6O_4S$ (486.50): C, 59.25; H, 3.73; N, 17.27%. Found: C, 59.12; H, 3.58; N, 17.13%.

2-(3-((*E*)-((*E*)-5-(((1*H*-1,2,4-triazol-3-yl)amino)methylene)-4-oxothiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindoline-1,3-dione (14). A mixture of the enamine **13** (2.4 g, 5 mmol) and 3-amino-1,2,4-triazol (0.42 g, 5 mmol) in acetic acid (20 mL) containing anhydrous NaOAc (10 mmol) was refluxed for 18 h. The reaction mixture was cooled to room temperature then poured onto ice–cooled water. The precipitate was filtered off and washed with H_2O and the resulting crude product was purified by recrystallization from dioxane as brown crystals, yield: 77%, mp > 300 °C; IR (KBr): ν (cm^{-1}) 1657, 1695 and 1701 (3C=O_{str}) and 3158-3211 (2NH_{str}). ^1H NMR (300 MHz, DMSO–d_6): δ 4.01 (d, 1H, *J* 10.8 Hz, =CH–N*H*), 6.86 (*d*, 1H, *J* 10.8 Hz, =CH), 7.21–7.49 (*m*, 10H, 9 H–Ar, H–$5_{Pyraz.}$), 8.44 (br. *d,* 1H, H–$5_{Triaz.}$), 10.03 (br. *s*, 1H, N–$H_{Thiaz.}$), 12.41 (*s*, 1H, N–$H_{Triaz.}$); MS: *m/z,* 525.0 (M^+, 35%). Anal. Calcd for $C_{24}H_{15}N_9O_4S$ (525.50): C, 54.85; H, 2.88; N, 23.99%. Found: C, 54.39; H, 2.78; N, 23.85%.

(*E*)-2-(3-(9*H*-Naphtho[1,2-*e*]thiazolo[4,5-*b*][1,4]oxazin-9-ylideneamino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindoline-1,3-dione (17). A mixture of of **7 (**4.31 g, 0.01 mol), α-nitroso-β-naphthol (1.73 g

0.01 mol) and piperidine (0.1 mL) in EtOH (30 mL) was refluxed for 8 h. The reaction mixture was filtered on hot, concentrated and cooled. The crude product was purified by recrystallization from EtOH to afford **17** (62%) as yellow crystals. mp 293-295 °C; IR (KBr): ν (cm^{-1}) 1657, 1695, 1701 (3 C=$O_{str.}$), 1630 (C=N_{str}). ^{1}H NMR (300 MHz, DMSO–d_6): δ 7.21–7.49 (*m*, 11H, 10 H–Ar, H–$5_{Pyraz.}$); MS: *m/z,* 568.0 (M^+, 45%). Anal. Calcd for $C_{31}H_{16}N_6O_4S$ (568.56): C, 65.49; H, 2.84; N, 14.78%. Found: C, 65.28; H, 2.68; N, 14.74%.

2-(3-((*E*)-((*E*)-(4-oxo-5-(2-phenylhydrazono)thiazolidin-2-ylidene)amino)-1-phenyl-1*H*-pyrazole-4-carbonyl)isoindo-line-1,3-dione (18). $NaNO_2$ (0.76 g, 1.0 mmol) in cold H_2O (15 mL) was added dropwise during a period of 15 min to a mixture of aniline (1.0 mmol) in EtOH (10 mL) containing conc. HCl (3.0 mL). Then, the mixture was added to a well stirred solution of **7** (4.31 g, 0.01 mol) in ice–cooled EtOH (10 mL) containing NaOAc (2.0 g, 0.024 mol) and stirring was continued overnight at rt. The resulting product formed was collected by filtration, washed by H_2O and recrystallized from EtOH to afford **16** (65%) as yellow crystals. mp 193–195 ºC; IR (KBr): ν (cm^{-1}) 1630 (C=$N_{str.}$), 1657, 1695, 1701 (3 C=$O_{str.}$), 3158–3211 (2 N–$H_{str.}$); ^{1}H NMR (300 MHz, DMSO–d_6): δ 6.91–7.48 (m, 15H, 14 H–Ar, H–$5_{Pyraz.}$), 10.01 (s, 1H, N–H) and 11.12 (*s*, 1H, N–H). MS: *m/z,* 535.0 (M^+, 40%). Anal. Calcd for $C_{27}H_{17}N_7O_4S$ (535.53): C, 60.55; H, 3.20; N, 18.31%. Found: C, 60.38; H, 3.18; N, 18.02%.

(*E*)-6-(4-(1,3-Dioxoisoindoline-2-carbonyl)-1-phenyl-1*H*-pyrazol-3-ylimino)-3-oxo-2-phenyl-2,3,5,6-tetrahydrothiazolo[5,4-*c*]pyridazine-4-carbonitrile (21). A mixture of **18** (0.53 g, 1.0 mmol), ethyl cyanoacetate (0.13 mL, 1.0 mmol) and piperidene (0.1 mL) in EtOH (20 mL) was refluxed for 4 h. The mixture was filtrated and the crude powder was recrystallized from (dioxane–H_2O, 2:1) to afford **19** (60%) as yellow crystals. mp 216–18 ºC; IR (KBr): ν (cm^{-1}) 1630 (C=$N_{str.}$), 1657, 1692, 1704 (3 C=O), 2212 (C≡N) and 3128 (NH); ^{1}H NMR (300 MHz, DMSO–d_6): δ 6.91–7.48 (*m*, 15H, 14 H–Ar, H–$5_{Pyraz.}$), 10.01 (s, 1H, N–H). MS: *m/z,* 584.0 (M^+, 57%). Anal. Calcd for $C_{30}H_{16}N_8O_4S$ (584.56): C, 61.64; H, 2.76; N, 19.17%. Found: C, 61.48; H, 2.43; N, 19.01%.

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