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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Solvent-free, one-pot synthesis and biological evaluation of some new dipyrazolo [3,4-*b*:4′,3′-*e*]pyranylquinolones and their precursors

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Abstract One-pot synthesis of 24 new compounds, belonging to three families; dipyrazolo[3,4-*b*:4′,3′-*e*]pyranylquinolones **7a–h** and its precursors (pyrazolonylidene) methylquinolones **5a–h** and 4,4′-[(quinolinyl)methylene]bispyrazols **6a–h**, 8 from each, has been achieved in the presence of catalyst tetrabutylammonium hydrogen sulfate (TBA–HS) in solvent-free conditions. In addition to assuring chromatography-free product isolation, this method had also allowed the reaction to proceed in a regio-selective manner provided the temperature and amount of pyrazolone are varied. At 100 °C, while 1:1 mixture of aldehyde **3** and pyrazolone **4** underwent Knoevenagel condensation, same reactants taken in ratio of 1:2 mainly domino/Knoevenagel–Michael reaction. At 120 °C, however, the domino/Knoevenagel–Michael-adducts converted into cyclized product, highlighting a new domino/Knoevenagel–Michael-cyclization synthetic sequence. The structure of all heterocycles has been confirmed by mass, IR and NMR spectral data. Based on 2D NMR NOESY experiment, it was also confirmed that the formation of only 'Z' configuration of Knoevenagel alkene took place in the transformation. All are good antitubercular agents as they were found to be active against *M. tuberculosis H37RV*, in addition to being found active against three Gram-positive (*Streptococcus pneumoniae, Clostridium tetani, Bacillus subtilis*) and three Gram-negative (*Salmonella typhi, Vibrio cholerae, Escherichia coli*) bacteria, respectively.

Keywords Knoevenagel–Michael · Tetrabutyl ammonium hydrogen sulfate · 3-Methyl-1-phenyl-5-pyrazolone · Bis-Pyrazole · *N*-Allyl quinolone

Introduction

Pyrazolone is a subunit of many biologically active compounds (McDonald *et al.*, 2006; El-Nagdi *et al.*, 1987). Drugs incorporating this unit have been a continuous source of known anti-anxiety (DeWald *et al.*, 1977), anti-inflammatory, antipyretic, analgesic (El-Hawash Soad *et al.*, 2006), anti-depressant (Bailey *et al.*, 1985), anti-convulsant (Abdel–Aziz *et al.*, 2009) and hypnotic agents (Sugiura *et al.*, 1977). For example, 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) have remarkable anti-inflammatory, antipyretic (Behr *et al.*, 1967), gastric secretion stimulatory (Rosiere *et al.*, 1951), antibacterial (Mahajan *et al.*, 1991), and antifilarial activities (Chauhan *et al.*, 1993). Several fungicides (Singh and Singh, 1991), pesticides (Londershausen, 1996), insecticides (Lube, 1970), dyestuffs (Garnovskii *et al.*, 2004), and chelating and extracting reagents used for different metal ions are potential candidates (Parmar and Teraiya, 2009; Parmar *et al.*, 2010, 2011a). Tendency of bis-pyrazole to coordinate many metal ions via its 5-ol oxygen has played significant role in metal extraction studies (Parmar and Teraiya, 2009; Parmar *et al.*, 2010).

Condensed pyrazoles, on the other hand, are equally significant (Baraldi *et al.*, 2012; Verheijen *et al.*, 2009). Many pyrano[2,3-*c*]pyrazoles are known in this group (EL-Nagdi *et al.*, 1990; Kuo *et al.*, 1984). In recent past, fused azoles have also emerged as intensive research topic (EL-Nagdi *et al.*, 1990; Kuo *et al.*, 1984; Koyama and Umezawa,

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1965; Elmoghayar *et al.*, 1984; Anderson and Jones, 1984). Finally, bis-pyrazolopyrans and their analogues have revealed an excellent activity against pest des petits ruminant virus (PPRV) (Sujatha *et al.*, 2009), a useful biological application.

Knoevenagel adducts arylidenepyrazolones formed in the first step transform into bis-pyrazoles via Michael addition reaction (Singh and Singh, 1984; Singh and Singh, 1991; Londershausen, 1996). Conventionally, their syntheses take a longer reaction time in refluxing water or other refluxing solvents like ethanol or benzene, in addition to affording moderate yields. Product isolation step is also tedious part of conventional methods (Gunasekaran *et al.*, 2011; Tale *et al.*, 2011; Yao *et al.*, 2007). One-pot Knoevenagel–Michael addition of aldehyde with 2 equivalents of *3H*-pyrazol-3-ones in tandem is another approach (Sujatha *et al.*, 2009; Pavlov *et al.*, 1998; Buzykin and Lonshchakova, 1971; Wang *et al.*, 2005; Elinson *et al.*, 2008; Niknam *et al.*, 2010). In piperidine, however, yields were in the 15–30 % range (Singh and Singh, 1984). Improved protocols seemed to be in water or ethanol in the presence of electrolyte NaBr (Elinson *et al.*, 2008), surfactant sodium dodecyl sulfate (SDS) (5 mol %) (Wang *et al.*, 2005), Lewis acid ceric ammonium nitrate (CAN) (Sujatha *et al.*, 2009) or $[Cu(3,4\text{-tmtppa})](MeSO_4)_4$ (Sobhani *et al.*, 2009) and recyclable catalyst silica-bonded *S*-sulfonic acid (SBSSA) (Niknam *et al.*, 2010). Other method utilized acetic acid and ETBA (Shi *et al.*, 2005). Li *et al.* (1995, 1997).utilized a solid-state for the synthesis of 4,4′-(arylmethylene)bis(*1H*-pyrazol-5-ols) Bai *et al.* (2004) reported catalyst-free microwave irradiation. As Brønsted acid, ionic liquid 1-methylimidazolium hydrogen sulfate $[HMIM]HSO_4$ though promotes reaction it takes a longer reaction time (Zang *et al.*, 2011). In spite of vast literature reports, however, no tetrabutylammonium hydrogen sulfate (TBA–HS) has been tried and explored in the strategy. Moreover, several aldehydes (Sujatha *et al.*, 2009; Pavlov *et al.*, 1998; Buzykin and Lonshchakova, 1971; Wang *et al.*, 2005; Elinson *et al.*, 2008; Niknam *et al.*, 2010; Ballini *et al.*, 2003; Macquarrie *et al.*, 2003) have been tried, but no insoluble quinoline-3-carbaldehydes. Insoluble aldehyde is thus limitation of reported protocols along with other issues like yields, reaction time, high temperature and tedious workup procedure (Sujatha *et al.*, 2009; Pavlov *et al.*, 1998; Buzykin and Lonshchakova, 1971; Wang *et al.*, 2005; Elinson *et al.*, 2008; Niknam *et al.*, 2010; Li *et al.*, 1995, 1997; Shi *et al.*, 2005; Sobhani *et al.*, 2009; Niknam *et al.*, 2010). Use of solid catalysts environmentally is of a great interest in chemistry and industry as they offer them simplicity in handling, safety of disposal, and less industrial corrosion (Michail *et al.*, 2011; Fan *et al.*, 2006). The reactive centers because of highly mobility have an advantage of being recyclable, too.

Quinolone-incorporated heterocycles (Uchida *et al.*, 1985; Hong *et al.*, 2001; Parmar *et al.*, 2012a), as new molecular templates, are anticipated to have promising pharmaceutical activities especially antioxidant and anticancer (Hong *et al.*, 2001; Parmar *et al.*, 2012a, b, c; Faber and Kappe, 1984; Chen *et al.*, 2004; Ukrainets *et al.*, 1993). Both 3,4-double bond and 2-oxo functionalities in 2-quinolone unit are well known for hydroxyl radical scavenging properties (Uchida *et al.*, 1985). Rebamipide, for example, is effective antioxidant as well as antiulcer agent (Hong *et al.*, 2001). Alkylation in general and allylation in particular improves affinity of resulted heterocycles towards the cholecystokinin (CCK2) receptor that has been involved in many pathological situations (Lattmann *et al.*, 2002).Those which include anxiety (Bain and Candillis, 2000) and panic (Tullio *et al.*, 2000) particularly, are relevant targets to therapeutic interventions. Considering the biological significance of quinoline-based compounds and a part of our ongoing interest (Parmar *et al.*, 2011b, 2012a, b; c), it was therefore planned to prepare some new pyrazolonylidenemethylquinolones **5a–h**, 4,4′-[(quinoline-3-yl)methylene]bis(1*H*-pyrazol-5-ols) **6a–h**, and dipyrazolo[3,4-*b*:4′,3′-*e*]pyranylquinolones **7a–h**.

Results and discussion

Chemistry

First, we treated quinolines **2a–b** obtained (from acetanilides **1a–b)** via Vilsmeier–Haack reaction with 70 % acetic acid (Scheme 1). Second, the quinolone obtained was treated with allyl bromide in the presence of potassium carbonate suspended in DMF (dimethylformamide) (Parmar *et al.*, 2012a). Finally, *N*-allyl-2-quinolone-3-carbaldehyde **3** thus obtained was heated with corresponding pyrazolone **4** taken in varied amounts in the presence of 20 mol % tetrabutyl ammonium hydrogensulftae (TBA–HS) under solvent-free conditions. At 100 °C, while 1:1 mixture of reactants (**3** and **4** each in 1.12 mmol) results in (pyrazolonylidene)methylquinolones **5a–h** formation via Knoevenagel condensation, their 1:2 mixture (**4** in 2.24 mmol and **3** in 1.12 mmol) in 4,4′-[(quinoline-3-yl)methylene]bis(1*H*-pyrazol-5-ols) **6a–h** formation via Knoevenagel–Michael reaction (Scheme 2). On heating the reaction mass containing Knoevenagel–Michael products further at 120 °C, cyclization of the products **6a–h** was observed, highlighting a new tandem Knoevenagel–Michael-cyclization route to dipyrazolo [3,4-*b*:4′,3′-*e*]pyranylquinolones **7a–h** products. The protocol had advantageously employed no chromatography for product separation, and the workup procedure used was very simple. In our early work, TBA–HS has been successfully used to promote domino/

Knoevenagel-*hetero*-Diels–Alder reaction in refluxing xylene (Parmar *et al.*, 2011b, 2012b). Investigating further, we in present work described the application of this PTC catalyst in solvent-free environment too, highlighting a new greener approach to access heterocycles (Table 1; Scheme 2).

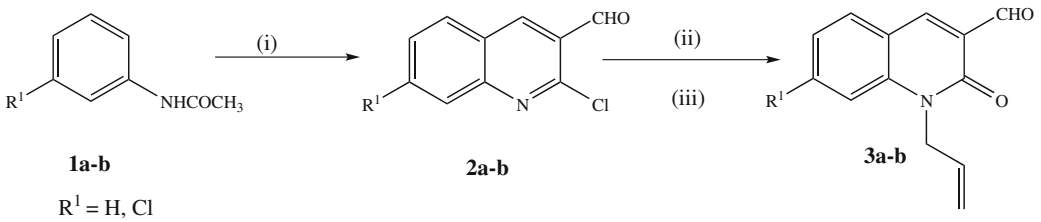
The mechanism of the entire domino reaction begins with the formation of reactive species tetrabutylammonium pyrazolonate. With quinolone-3-carbaldehyde, it formed Z-Knoevenagel alkene **5** at 100 °C. Consuming second molecule of pyrazolone, this Knoevenagel-adduct **5** then transformed into Michael-adducts **6**. Finally, in the influence of TBA–HS, compound **6** gave cyclized products **7** at 120 °C (Scheme 3).

The recyclability of the catalyst was also tested, confirmed and established by re-using the recovered catalyst, at least four times without the significant loss of its activity (Fig. 1). To recover the catalyst, the reaction mass, after being dissolved in methanol, was first poured into ice cold water to precipitate the product. The solid products were then isolated through ordinary filtration. Heating the filtrate in vacuum at 70 °C evaporated the fluid aqueous-organic mixture and gave residues of TBA–HS in 6 h.

The structure of all newly synthesized compounds **5a–h**, **6a–h** and **7a–h** was confirmed by mass, IR, ^{1}H NMR and ^{13}C NMR spectral data. In the IR of all, the band at around 1,640 cm^{-1} can be assigned to amide linkage of quinolone moiety. At a small distance, the second band at around 1,673 cm^{-1} in all Knoevenagel-adducts **5** is assigned to pyrazolone moiety. Formation of all new families of compounds; **5**, **6** and **7**, can be asserted from the spectral data. In Michael-adduct **6a**, broad bands that appeared in the region around 3,418 cm^{-1} confirm the presence of pyrazolol (enol form) moieties. In ^{1}H NMR, the singlet at δ 2.40 in **5a**, at 2.35 in **6a** and at 2.29 in **7a** confirms the presence of methyl protons at pyrazole ring. A complete shift of singlet arylidine CH proton from δ 8.19 in **5a** to δ 5.16 a little bit higher in **6a** indicate the formation of Michael-adduct **6a** from Knoevenagel alkene **5a.** The same could also be traced out from ^{13}C NMR which evidenced the complete transformation of alkene sp^2 CH (appeared in the aromatic region δ 120–150 of **5a)** into sp^3 CH (appeared at δ 29.44 in **6a)**. In the same way, the cyclization of Michael-adduct could also be evidenced from observing the disappearance of peaks δ 12.56 and δ 14.29 of **6a** (assigned to hydroxyl groups) in **7a**. Further, a

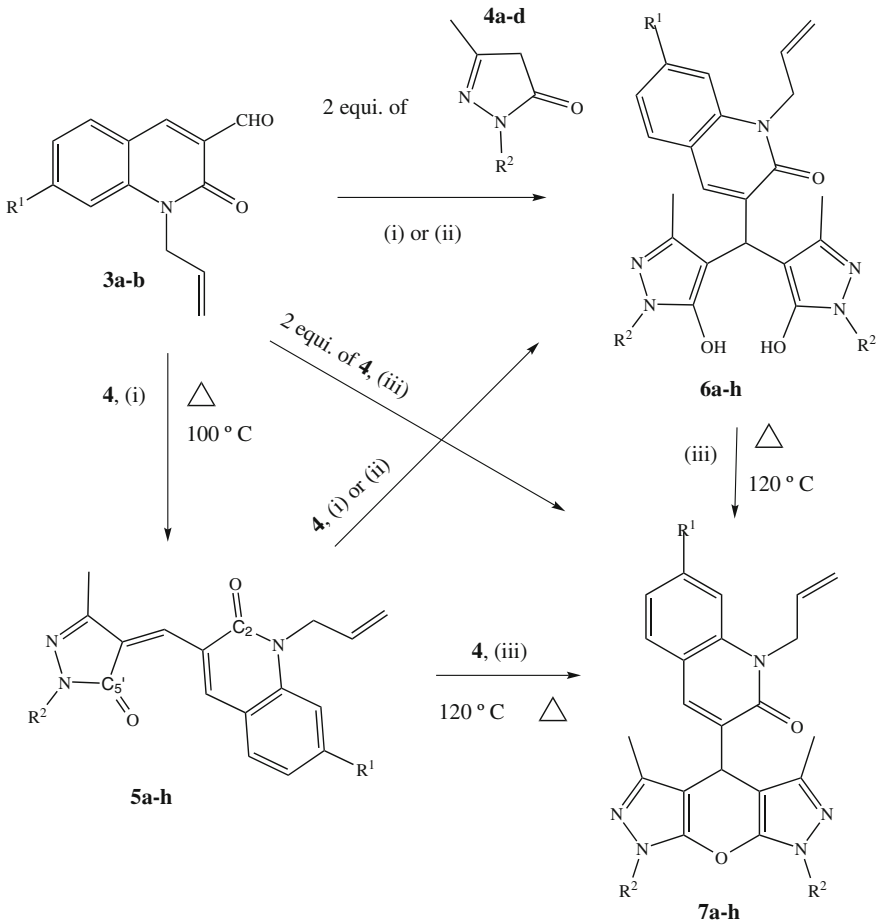
Table 1 Synthesis of Knoevenagel-adducts pyrazolonylidenemethylquinolones **5a–h**, Michael-adducts 4,4′-[(quinoline-3-yl) methylene]bis(*1H*-pyrazol-5-ols) **6a–h**, and cyclized products dipyrazolo[3,4-*b*: 4′,3′-*e*]pyranylquinolones **7a–h**

Entry	Compounds	R^1	R^2	Time	Yield %
1	**5a**	H	Ph	20 min	90
2	**5b**	H	2-Cl Ph	25 min	87
3	**5c**	H	3-Cl Ph	20 min	91
4	**5d**	H	2,5-Cl_2 Ph	25 min	88
5	**5e**	Cl	Ph	20 min	91
6	**5f**	Cl	2-Cl Ph	25 min	89
7	**5g**	Cl	3-Cl Ph	30 min	90
8	**5h**	Cl	2,5-Cl_2 Ph	20 min	93
9	**6a**	H	Ph	2.0 h	92
10	**6b**	H	2-Cl Ph	1.5 h	91
11	**6c**	H	3-Cl Ph	2.0 h	93
12	**6d**	H	2,5-Cl_2 Ph	1.5 h	94
13	**6e**	Cl	Ph	2.0 h	92
14	**6f**	Cl	2-Cl Ph	2.0 h	91
15	**6g**	Cl	3-Cl Ph	2.0 h	93
16	**6h**	Cl	2,5-Cl_2 Ph	1.5 h	92
17	**7a**	H	Ph	1.5 h	89
18	**7b**	H	2-Cl Ph	2.0 h	85
19	**7c**	H	3-Cl Ph	1.5 h	88
20	**7d**	H	2,5-Cl_2 Ph	1.5 h	87
21	**7e**	Cl	Ph	1.5 h	89
22	**7f**	Cl	2-Cl Ph	2.0 h	86
23	**7g**	Cl	3-Cl Ph	2.0 h	85
24	**7h**	Cl	2,5-Cl_2 Ph	1.5 h	88



Scheme 1 Synthesis of *N*-allyl-2-quinolone-3-carbaldehyde. Reagents and conditions: (*i*) DMF, $POCl_3$, 75–80 °C, 8 h; (*ii*) 70 % AcOH, reflux, 4 h; (*iii*) allyl bromide, K_2CO_3, DMF, 12 h, RT

Scheme 2 Knoevenagel–Michael–cyclization reaction. Reagents and conditions: (*i*) 20 % TBA–HS, solvent-free 100 °C; (*ii*) 5 % SLS, water, reflux; (*iii*) 20 % TBA–HS, solvent-free, 120 °C

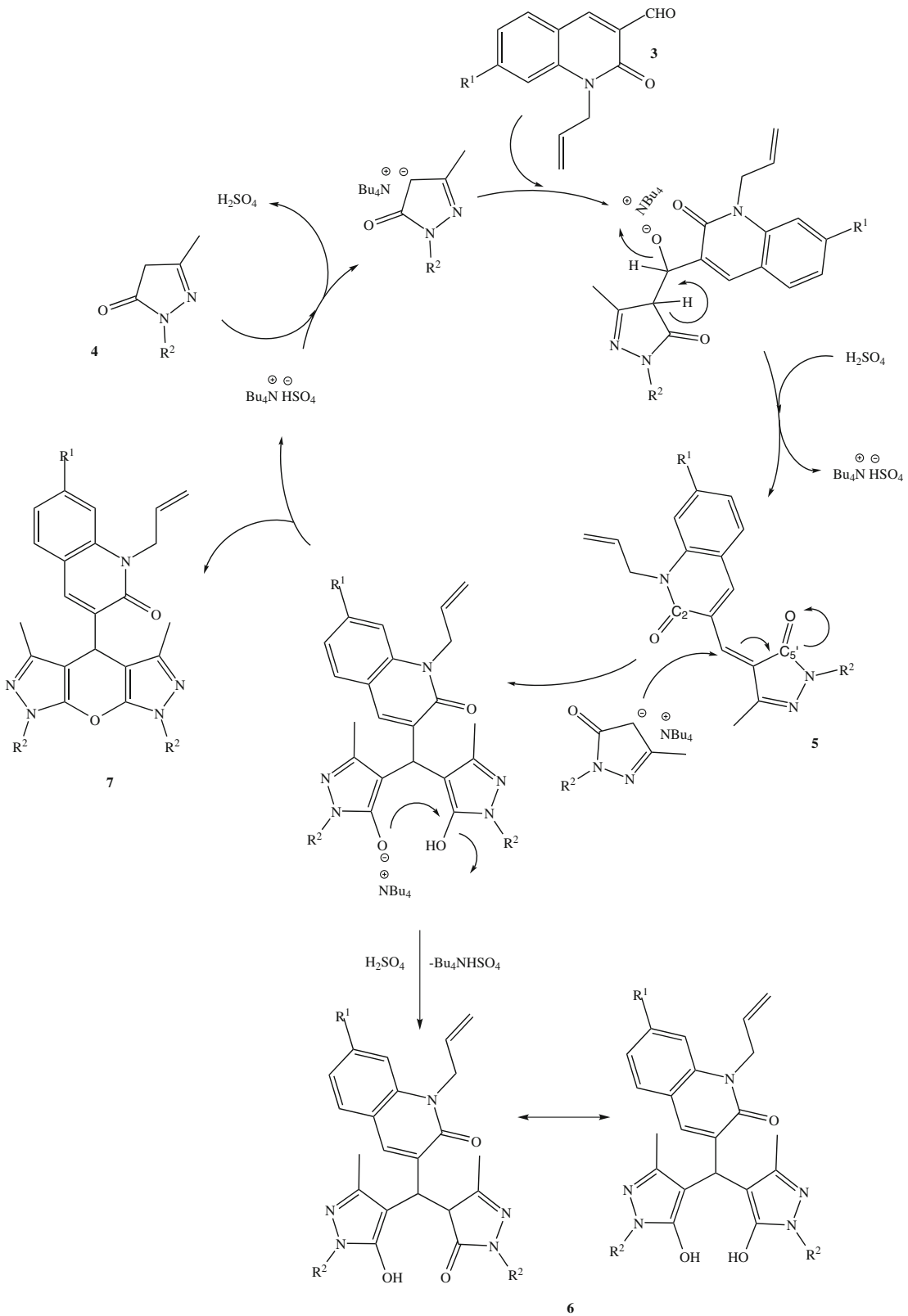


multiplet at δ 6.03, a doublet at δ 5.01 ($J = 2.0$), and two doublets; one at 5.17 with $J = 17.2$ and second at δ 5.29 with $J = 10.4$ confirm the presence of allyl protons in **5a**. The same can be concluded from ^{13}C NMR wherein both CH_2 gave characteristic peaks; one at δ 45.44 and second at δ 117.50.

Besides above, the 2D NMR NOESY spectrum was also taken to assign E or Z configuration to Knoevenagel alkene **5e** generated from the *N*-allyl-2-quinolone-3-carbaldehydes **3b** and pyrazolone **4a**. As could be seen from the NOESY, it showed the apparent correlation between pyrazolone methyl (δ 2.40) protons and that of alkene sp^2 CH, confirming the Z configuration. Correlation of neither alkene sp^2 CH (δ 8.14) nor pyrazolone methyl protons with that of quinoline nitrogen ring too rules out the possibility of E-configuration. The proposed structure of **5e** has been depicted as Fig. 2.

Antimicrobial activity

The in vitro antimicrobial activity of all the compounds were determined against three Gram-positive *Streptococcus pneumoniae* (MTCC 1936), *Clostridium tetani* (MTCC



Scheme 3 Plausible mechanism for TBA–HS catalyzed Knoevenagel–Michael-cyclization reaction

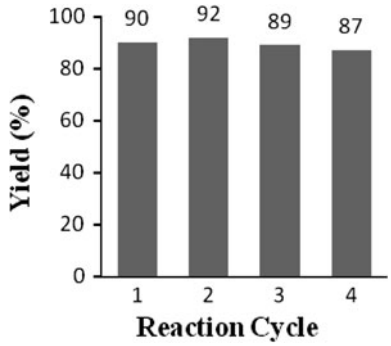


Fig. 1 Recyclability of catalyst TBA–HS

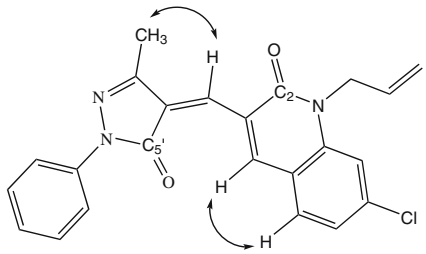


Fig. 2 Characteristic NOESY of **5e**

449), *Bacillus subtilis* (MTCC 441), three Gram-negative *Salmonella typhi* (MTCC 98), *Vibrio cholerae* (MTCC 3906), *Escherichia coli* (MTCC 443) bacteria and two *Aspergillus fumigatus* (MTCC 3008), *Candida albicans* (MTCC 227) fungi by the broth microdilution MIC (minimum inhibitory concentration) (Shadomy and Pfaller MA 1991) method according to NCCLS (National Committee for Clinical Laboratory Standards). (NCCLS, 2000) Strains employed for the activity were procured from [MTCC (Micro Type Culture Collection)] Institute of Microbial Technology, Chandigarh. Mueller–Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose Broth used for fungal nutrition. Bacterial strains were primarily inoculated into Mueller–Hinton agar and, after overnight growth, a number of colonies were directly suspended in saline solution until the turbidity matched the turbidity of the McFarland standard (approximately 10^8 CFU/mL), i.e., inoculum size for test strain was adjusted to 10^8 CFU/mL (colony forming unit) per milliliter well by comparing the turbidity (turbidimetric method). Similarly, fungi were inoculated on Sabouraud Dextrose Broth; the procedures of inoculum standardization were also similar. DMSO was used as diluents/vehicle to get desired concentration of compounds to test upon standard microbial strains, i.e., the compounds were dissolved in DMSO and the solutions were diluted with a culture medium. Each compound and standard drugs were diluted obtaining 2,000 μg/mL concentration, as a stock solution. By further progressive dilutions with the test medium, the required concentrations were obtained for primary and secondary screening. In primary screening 1,000, 500, and 250 μg/mL concentrations of the compounds were taken. The active compounds found in this primary screening were further diluted to obtain 200, 100, 62.5 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Briefly, the control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism. The tubes are then put for incubation at 37 °C for 24 h for bacteria and 48 h for fungi. Growth or a lack of growth in the tubes containing the antimicrobial agent was determined by comparison with the growth control, indicated by turbidity. The lowest concentration that completely inhibited visible growth of the organism was recorded as the minimum inhibitory concentration (MIC, μg/mL), i.e., the amount of growth from the control tube before incubation (which represents the original inoculum) is compared. A set of tubes containing only seeded broth and the solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth. All bioassays were repeated at least three times and the calculated error margin value was ±2 μg/mL. Protocols are summarized in Table 2 as the minimum inhibitory concentration (MIC, μg/mL).

Screening results showed that all Knoevenagel-adducts **5a–h,** Michael-adducts **6a–h**, and corresponding cyclized products dipyrazolo[3,4-*b*:4′,3′-*e*]pyranylquinolones **7a–h** are possessing good antibacterial activity against three Gram-positive (*Streptococcus pneumoniae, Clostridium tetani, Bacillus subtilis*) and three Gram-negative (*Salmonella typhi, Vibrio cholerae, Escherichia coli*) bacteria, in comparison to their antifungal activity against two fungus *Aspergillus fumigatus* and *Candida albicans*. The results are expressed in minimum inhibition concentration (MIC) measured in μg/mL (Table 2). More than 80 % of the total compounds tested are active against each type of Gram-positive and Gram-negative bacteria with a MIC in the range 250–50, except the ones against *Salmonella typhi* bacteria. Here, the highest 95.8 % of total screened candidates were potent particularly against type of these bacteria. Analyzing in terms of MIC, it was further inferred that majority have MIC equal to 200. Those with lowest MIC (50–62.5 μg/mL) include; **7d** against Gram-positive *Streptococcus pneumoniae* bacteria, and **5g** and **7a** against Gram-negative *Escherichia coli* bacteria, resembling the standard drug chloramphenicol. Additionally, compounds **5g** and **7d** are much closer to standard ciprofloxacin in terms of their potency against former type bacteria.

Table 2 Antibacterial and antifungal test results (MIC)

Compounds	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S.p. MTCC 1936	*C.t.* MTCC 449	*B.s.* MTCC 441	*S.t.* MTCC 98	*V.c.* MTCC 3906	*E.c.* MTCC 443	*A.f.* MTCC 3008	*C.a.* MTCC 227
5a	**150**	500	200	**100**	250	**62.5**	>250	>250
5b	250	500	250	200	**100**	500	>250	>250
5c	200	**100**	250	200	200	250	>250	>250
5d	250	250	**100**	**100**	200	250	>250	>250
5e	**100**	250	**100**	250	200	250	>250	>250
5f	500	500	500	250	500	500	>250	>250
5g	200	**100**	500	**62.5**	200	**100**	>250	>250
5h	250	**100**	200	**100**	**125**	**100**	>250	**250**
6a	500	**100**	500	200	500	250	>250	>250
6b	**125**	250	200	**100**	500	200	>250	>250
6c	250	200	250	200	200	500	>250	>250
6d	200	**100**	**125**	200	**100**	250	>250	>250
6e	250	200	250	500	200	500	>250	>250
6f	250	**100**	**125**	200	200	200	>250	**250**
6g	**100**	200	200	200	250	250	>250	>250
6h	250	500	250	**100**	250	**100**	>250	>250
7a	**100**	**100**	500	**62.5**	**125**	250	>250	>250
7b	500	250	200	200	**100**	500	>250	>250
7c	250	200	250	250	200	250	>250	>250
7d	**50**	250	200	**100**	500	250	>250	>250
7e	250	**100**	200	200	200	**100**	>250	>250
7f	200	**100**	250	250	200	200	>250	**250**
7g	500	250	500	200	500	**100**	>250	>250
7h	200	250	200	200	250	200	>250	>250
[A]	100	250	250	100	100	100	–	–
[B]	10	50	100	10	10	10	–	–
[C]	50	50	50	50	50	50	–	–
[D]	50	100	50	25	25	25	–	–
[E]	–	–	–	–	–	–	100	500
[F]	–	–	–	–	–	–	100	100

Bold numbers indicate relatively good activities, which are close to standards

MIC is minimum inhibitory concentration in μg/mL as average of triplicate results, all with standard deviation ± 2 μg/mL

S.p. Streptococcus pneumoniae, *C.t. Clostridium tetani*, *B.s. Bacillus subtilis*, *S.t. Salmonella typhi*, *V.c. Vibrio cholerae, E.c. Escherichia coli*, *A.f. Aspergillus fumigatus*, *C.a. Candida albicans*, *[A]* ampicillin, *[B]* norfloxacin, *[C]* chloramphenicol, *[D]* ciprofloxacin, *[E]* griseofulvin, *[F]* nystatin

Antitubercular activity

A screening was conducted at 250 μg/ml against *M. tuberculosis* H37Rv following a Lowenstein–Jensen (L-J) MIC method. Compounds were added to liquid L-J medium and then media were sterilized by inspissations method. A culture of *M. tuberculosis* H37Rv grown on L-J medium was harvested in 0.85 % saline in bijou bottles. DMSO was used as vehicle to get a desired concentration. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 12, 22, and finally 28 days incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37Rv. The standard strain *M. tuberculosis* H37Rv was tested with known drugs; isoniazide, fluconazole and miconazole. The screening test results are summarized as % inhibition relative to standard drugs.

All the compounds were also screened against *M. Tuberculosis H37RV bacteria*. The screening test results were obtained and examined running L.J. method (NCCLS,

Table 3 Antitubercular test results

Compounds	Growth of inhibition[a] (%)	Compounds	Growth of inhibition[a] (%)
5a	**92**	**6f**	23
5b	**86**	**6g**	74
5c	27	**6h**	51
5d	46	**7a**	39
5e	35	**7b**	43
5f	**91**	**7c**	62
5g	44	**7d**	18
5h	26	**7e**	46
6a	**88**	**7f**	71
6b	80	**7g**	30
6c	65	**7h**	28
6d	39	Standard[b]	99
6e	**87**		

Bold numbers indicate relatively good activities, which are close to standards

[a] A concentration 250 μg/mL of each was used against *M. Tuberculosis H37RV* bacteria, and standard deviation (SD) of measuring % growth inhibition thrice was in the 2–5 % range

[b] Standard antimicrobials used were: isoniazide (0.2 μg/mL), fluconazole (>256 μg/mL) and miconazole (>256 μg/mL)

2009). Test results are shown in Table 3. Here, 250 μg/mL of each compound was tested. From the test results, it divulges that compounds **5a** and **5f** are good in antitubercular activity as their percent growth inhibitions showed 91 and 92 %, respectively. For others **5b**, **6a** and **6e**, the percent growth inhibition lies in the 86–88 % range, indicating that they are less potent than the former ones. Nevertheless, these results when analyzed in terms of concentration are very close to the ones that standard drugs like fluconazole (>256 μg/mL) and miconazole (>256 μg/mL) reveal.

Experimental

All solvents and reagents were used as supplied from commercial sources. The recorded melting points are uncorrected. IR spectra were recorded in KBr on Shimadzu FT-IR 8401 spectrometer and are reported in wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR as solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported as parts per million (ppm, δ) and referenced to the residual protic solvent. Coupling constants are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. The degree of substitution (C, CH, CH_2, and CH_3) was determined by the DEPT-135 method. The ESI mass spectra were measured on Shimadzu LCMS-2010 spectrometer. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA). TLC was performed on Merck 60 F254 precoated silica plates, spots were detected either by UV (254 nm, 366 nm) or dipping into a permanganate [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5 % in H_2O), H_2O (300 mL)] or an anisaldehyde solution [3 % *p*-methoxybenzaldehyde and 1 % H_2SO_4 in MeOH] or 2,4 dinitro phenyl hydrazine solution [2,4-DNP (12 g), conc. H_2SO_4 (6 mL), water (8 mL), EtOH (20 mL)] followed by heating.

Synthesis of *N*-allylquinolone-3-carbaldehyde **3a–b** (Parmar *et al.*, 2012a)

*Synthesis of quinoline **2a–b***

$POCl_3$ (9 ml, 98.28 mmol) was added drop wise to DMF (2.7 ml, 34.65 mmol) whilst maintaining the temperature at 0–5 °C. The mixture was stirred for about 5 min. Acetanilide **1a–b** (10.37 mmol) was then added and the resulting solution heated for 8 h at 75–80 °C. The reaction mixture was cooled to room temperature and then poured into crushed ice with stirring. A pale yellow precipitate appeared immediately and was filtered and washed with water and then dried.

Synthesis of quinolone

A suspension of aldehyde **2a–b** (1 mmol) in 70 % acetic acid (10 ml) was heated under reflux for 4–6 h. The complication of the reaction was checked by TLC. Up on cooling the reaction mixture, a solid product precipitated out which was filtered, washed well with water, dried and purified by recrystallisation from DMF.

*Synthesis of N-allylquinolone **3a–b***

Allyl bromide (1.5 equiv.) and potassium carbonate (1.5 equiv.) were added to quinolones (1 mmol) in DMF (5 ml) and the reaction mixture was stirred at room temperature for 3–4 h. After completion (checked by TLC) the reaction mixture was poured into ice-cooled water (25 ml) whereupon a solid product precipitated out, which was filtered, washed well with water, dried and purified by recrystallisation from 70 % aqueous ethanol.

General procedure for the synthesis of Knoevenagel-adducts pyrazolonylidenemethylquinolones **5a–h**

N-Allyl quinolone **3a–b** (1.12 mmol), pyrazolone **4a–d** (1.12 mmol, 1 eq.) and TBA–HS (20 mol %) were well mixed in a round-bottom flask and heated to 100 °C for

20–35 min with constant stirring. After completion of the reaction as confirmed by TLC (ethyl acetate/*n*-hexane 3:7), reaction mass was cooled to room temperature, solid residue was obtained, which was crystallized from methanol to give the pure product **5**.

General procedure for the synthesis of Michael-adducts 4,4′-[(quinoline-3-yl)methylene]bis(1*H*-pyrazol-5-ols) **6a–h**

N-Allyl quinolone **3a–b** (1.12 mmol), pyrazolone **4a–d** (2.24 mmol, 2 eq.) and TBA–HS (20 mol %) were well mixed in a round-bottom flask and heated to 100 °C for 1.5–2.0 h with constant stirring. After completion of the reaction as checked by TLC (ethyl acetate/*n*-hexane 9.5:0.5), reaction mass was cooled to room temperature, solid residue was crystallized from methanol to give the product in pure form.

General procedure for the synthesis of cyclized products dipyrazolo[3,4-*b*:4′,3′-*e*]pyranylquinolones **7a–h**

N-Allyl quinolone **3a–b** (1.12 mmol), pyrazolone **4a–d** (2.24 mmol, 2 eq.) and TBA–HS (20 mol %) were well mixed in a round-bottom flask and heated to 120 °C for 1.5–2.0 h with constant stirring. After completion of the reaction as checked by TLC (ethyl acetate/*n*-hexane 9.5:0.5), reaction mass was cooled to room temperature, gave solid residue, which was crystallized from methanol to give the pure product.

1-Allyl-3-[(Z)-(3-methyl-1-phenyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene)methyl]quinolin-2(1H)-one ***5a*** Orange solid, yield 90 %, 390 mg, mp 182–184 °C; $R_f = 0.42$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,043, 2,919, 2,857, 1,673, 1,644, 1,597, 1,361, 1,495, 1,236, 1,149, 1,109, 1,022, 992, 780, 754, 691, 671; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3 H, CH_3), 5.01 (d, $J = 2.0$ Hz, 2H, CH_2), 5.17 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.29 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 6.03 (m, 1H, CH), 7.20–7.98 (m, 9H, Ar–H), 8.19 (s, 1H, –CH=), 10.30 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.23 (CH_3), 45.44 (CH_2), 114.78, 117.50 ($=CH_2$), 119.21, 120.31, 122.94, 123.57, 124.98, 128.76, 128.82, 131.20, 131.89, 133.32, 138.29, 140.54, 140.87, 146.04, 151.29 (arom.), 161.24 (C_2=O), 162.27 (C_5'=O); ESI–MS: *m/z*: 370.2 $(M+H)^+$, Anal Calcd for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37; Found: C, 74.64; H, 5.32; N, 11.55.

1-Allyl-3-{(Z)-[1-(2-chlorophenyl)-3-methyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene]methyl}quinolin-2(1H)-one ***5b*** Orange solid, yield 87 %, 412 mg, mp 178–180 °C; $R_f = 0.40$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,063, 2,920, 2,852, 1,686, 1,640, 1,599, 1,497, 1,365, 1,231, 1,154, 1,062, 993, 790, 758, 723, 699; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3 H, CH_3), 5.02 (d, $J = 1.6$ Hz, 2H, CH_2), 5.17 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.29 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 6.01 (m, 1H, CH), 7.24–7.80 (m, 8H, Ar–H), 8.26 (s, 1H, –CH=) 10.30 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.30 (CH_3), 45.45 (CH_2), 114.82, 117.51 ($=CH_2$), 120.38, 123.02, 123.65, 127.50, 127.56, 129.23, 129.76, 130.54, 131.16, 131.91, 132.26, 133.39, 135.04, 140.95, 141.26, 146.19, 151.57(arom.), 161.32 (C_2=O), 163.01 (C_5'=O); ESI–MS: *m/z*: 404.1 $(M+H)^+$, Anal Calcd for $C_{23}H_{18}ClN_3O_2$: C, 68.40; H, 4.49; N, 10.40; Found: C, 68.67; H, 4.65; N, 10.13.

1-Allyl-3-{(Z)-[1-(3-chlorophenyl)-3-methyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene]methyl}quinolin-2(1H)-one ***5c*** Red solid, yield 91 %, 431 mg, mp 180–182 °C; $R_f = 0.55$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,059, 2,928, 2,867, 1,688, 1,645, 1,593, 1,492, 1,368, 1,238, 1,153, 1,064, 990, 821, 788, 757, 674; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3 H, CH_3), 4.99 (d, $J = 2.0$ Hz, 2H, CH_2), 5.16 (d, $J = 16.8$ Hz, 1H, one of $=CH_2$), 5.24 (d, $J = 10.0$ Hz, 1H, the other of $=CH_2$), 6.00 (m, 1H, CH), 7.14–7.89 (m, 8H, Ar–H), 8.20 (s, 1H, –CH=), 10.31 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.23 (CH_3), 46.02 (CH_2), 115.63, 116.98 ($=CH_2$), 117.78, 120.52, 121.06, 122.15, 123.21, 123.87, 128.32, 129.11, 132.18, 133.46, 133.82, 135.32, 137.67, 139.04, 140.56, 147.13, 151.78 (arom.), 162.31 (C_2=O), 163.54 (C_5'=O); ESI–MS: *m/z*: 404.1 $(M+H)^+$, Anal Calcd for $C_{23}H_{18}ClN_3O_2$: C, 68.40; H, 4.49; N, 10.40; Found: C, 68.60; H, 4.73; N, 10.69.

1-Allyl-3-{(Z)-[1-(2,5-dichlorophenyl)-3-methyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene]methyl}quinolin-2(1H)-one ***5d*** Orange solid, yield 88 %, 452 mg, mp 202–204 °C; $R_f = 0.57$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,063, 2,924, 2,856, 1,685, 1,646, 1,596, 1,496, 1,364, 1,232, 1,152, 1,062, 993, 793, 784, 759, 684; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3 H, CH_3), 5.04 (d, $J = 1.6$ Hz, 2H, CH_2), 5.14 (d, $J = 16.8$ Hz, 1H, one of $=CH_2$), 5.23 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 6.03 (m, 1H, CH), 7.12-8.12 (m, 7H, Ar–H), 8.23 (s, 1H, –CH=), 10.34 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.45 (CH_3), 44.49 (CH_2), 116.01, 117.67 ($=CH_2$), 120.21, 123.27, 124.38, 127.36, 130.45, 130.83, 131.32, 131.83, 132.61, 133.42, 134.48, 135.49, 136.21, 140.42, 141.69, 145.23, 152.26 (arom.), 161.61 (C_2=O), 163.32 (C_5'=O); ESI–MS: *m/z*: 438.1 $(M+H)^+$, Anal Calcd for $C_{23}H_{17}Cl_2N_3O_2$: C, 63.03; H, 3.91; N, 9.59; Found: C, 63.31; H, 3.72; N, 9.77.

1-Allyl-7-chloro-3-[(Z)-(3-methyl-1-phenyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene)methyl]quinolin-2(1H)-one ***5e*** Red solid, yield 91 %, 410 mg, mp 208–211 °C; $R_f = 0.53$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,057, 2,921, 2,862, 1,680, 1,646, 1,599, 1,368, 1,490, 1,231, 1,138, 1,101, 1,031, 996, 790, 768, 682, 656; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3 H, CH_3), 4.97 (d, $J = 4.4$ Hz, 2H, CH_2), 5.18 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.33 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 6.01 (m, 1H, CH), 7.21–7.96 (m, 8H, Ar–H), 8.14 (s, 1H, –CH=), 10.29 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.62 (CH_3), 45.43 (CH_2), 116.62, 117.42 ($=CH_2$), 119.21, 120.43, 123.01, 124.86, 125.34, 127.56, 128.64, 128.82, 133.56, 136.32, 138.24, 140.27, 140.62, 146.41, 151.45 (arom.), 161.63 (C_2=O), 162.72 (C_5'=O); ESI–MS: *m/z*: 404.1 $(M+H)^+$,Anal Calcd for $C_{23}H_{18}ClN_3O_2$: C, 68.40; H, 4.49; N, 10.40; Found: C, 68.63; H, 4.76; N, 10.22.

1-Allyl-7-chloro-3-{(Z)-[1-(2-chlorophenyl)-3-methyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene]methyl}quinolin-2(1H)-one ***5f*** Orange solid, yield 89 %, 437 mg, mp 226–228 °C; $R_f = 0.44$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,053, 2,916, 2,851, 1,687, 1,651, 1,587, 1,485, 1,358, 1,229, 1,159, 1,061, 995, 812, 768, 716, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3 H, CH_3), 4.98 (d, $J = 4.4$ Hz, 2H, CH_2), 5.17 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.32 (d, $J = 10.8$ Hz, 1H, the other of $=CH_2$), 6.01 (m, 1H, CH), 7.23-7.72 (m, 7H, Ar–H), 8.21 (s, 1H, –CH=), 10.28 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.59 (CH_3), 44.86 (CH_2), 116.12, 117.51 ($=CH_2$), 121.41, 123.46, 123.35, 127.32, 127.64, 128.53, 130.66, 131.36, 131.84, 132.65, 133.43, 135.21, 136.76, 140.68, 141.32, 146.27, 151.47 (arom.), 161.43 (C_2=O), 162.79 (C_5'=O); ESI–MS: *m/z*: 438.1 $(M+H)^+$, Anal Calcd for $C_{23}H_{17}Cl_2N_3O_2$: C, 63.03; H, 3.91; N, 9.59; Found: C, 63.21; H, 4.09; N, 9.70.

*1-Allyl-7-chloro-3-{(Z)-[1-(3-chlorophenyl)-3-methyl-1,5-dihydro-*4H-pyrazol-5-one-4-ylidene]methyl}quinolin-2(1H)-one **5g** Orange solid, yield 90 %, 441 mg, mp 196–198 °C; $R_f = 0.49$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,064, 2,912, 2,869, 1,679, 1,649, 1,586, 1,493, 1,366, 1,227, 1,156, 1,054, 990, 816, 778, 721, 693; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 4.95 (d, $J = 4.4$ Hz, 2H, CH_2), 5.17 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.31 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 6.00 (m, 1H, CH), 7.15-8.05 (m, 7H, Ar–H), 8.35 (s, 1H, –CH=), 10.22 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.65 (CH_3), 45.13 (CH_2), 116.23, 117.20 ($=CH_2$), 117.87, 121.21, 121.87, 122.45, 123.37, 123.76, 127.56, 127.76, 128.56, 132.84, 133.34, 135.78, 136.67, 137.23, 138.12, 140.34, 146.54, 151.65 (arom.), 161.03 (C_2=O), 162.13 (C_5'=O); ESI–MS: *m/z*: 438.1 $(M+H)^+$,Anal Calcd for $C_{23}H_{17}Cl_2N_3O_2$: C, 63.03; H, 3.91; N, 9.59; Found: C, 62.87; H, 4.13; N, 9.76.

1-Allyl-7-chloro-3-{(Z)-[1-(2,5-dichlorophenyl)-3-methyl-1,5-dihydro-4H-pyrazol-5-one-4-ylidene]methyl}quinolin-2(1H)-one ***5h*** Orange solid, yield 93 %, 492 mg, mp 170–172 °C; $R_f = 0.75$ (ethyl acetate/*n*-hexane 3:7); IR (ν_{max}, cm^{-1}): 3,071, 2,928, 2,863, 1,688, 1,641, 1,590, 1,486, 1,361, 1,229, 1,159, 1,067, 991, 821, 788, 765, 664; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H, CH_3), 5.08 (d, $J = 2.0$ Hz, 2H, CH_2), 5.17 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.32 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 6.06 (m, 1H, CH), 7.02–7.90 (m, 6H, Ar–H), 8.14 (s, 1H, –CH=), 10.32 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.14 (CH_3), 46.01 (CH_2), 116.76, 117.50 ($=CH_2$), 120.89, 123.56, 124.52, 127.43, 127.23, 128.42, 129.71, 130.23, 131.12, 133.11, 134.67, 135.45, 136.91, 138.13, 140.46, 144.79, 146.12, 152.02 (arom.), 160.93 (C_2=O), 162.45 (C_5'=O); ESI–MS: *m/z*: 472.1 $(M+H)^+$,Anal Calcd for $C_{23}H_{16}Cl_3N_3O_2$: C, 58.43; H, 3.41; N, 8.89; Found: C, 58.76; H, 3.33; N, 9.01.

4,4′-[(1-Allyl-quinolin-2-one)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) ***6a*** White solid, yield 92 %, 585 mg, mp 198–200 °C; $R_f = 0.45$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,418, 3,073, 2,921, 1,639, 1,596, 1,415, 1,296, 1,023, 875, 795, 754, 689; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 6H, 2 CH_3), 4.93 (d, $J = 2.0$ Hz, 2H, CH_2), 4.97 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.12 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 5.16 (s, 1H, CH), 5.93 (m, 1H, CH), 7.19–8.03 (m, 15H, Ar–H), 12.56 (s, 1H, OH), 14.29 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 12.29 (CH_3), 29.44 (CH), 44.67 (CH_2), 115.21, 116.96 ($=CH_2$), 120.27, 121.20, 122.48, 126.06, 128.32, 129.30, 129.35, 130.31, 130.87, 132.44, 133.13, 135.58, 138.27, 147.08, 153.43 (arom.), 160.99 (C=O); ESI–MS: *m/z*: 544.2 $(M+H)^+$, Anal Calcd for $C_{33}H_{29}N_5O_3$: C, 72.91; H, 5.38; N, 12.88; Found: C, 73.21; H, 5.57; N, 12.62.

4,4′-[(1-Allyl-quinolin-2-one)methylene]bis[3-methyl-1-(2-chlorophenyl)-1H-pyrazol-5-ol] ***6b*** White solid, yield 91 %, 653 mg, mp 180–182 °C; $R_f = 0.44$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,410, 3,079, 2,921, 1,642, 1,596, 1,420, 1,300, 1,067, 883, 744, 657; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, 2 CH_3), 4.93 (m, 3H, CH_2 and one of $=CH_2$), 5.11 (m, 2H, the other of $=CH_2$ and CH), 5.92 (m, 1H, CH), 7.19-7.92 (m, 13H, Ar–H), 12.59 (s, 1H, OH), 14.09 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 12.43 (CH_3), 29.45 (CH), 44.71 (CH_2), 115.31, 116.59 ($=CH_2$), 119.73, 122.72, 127.43, 128.96, 129.46, 130.65, 130.69, 130.88, 131.76, 132.38, 132.86, 133.39, 134.75, 138.63, 140.95, 146.94, 153.21(arom.), 161.78 (C=O); ESI–MS: *m/z*: 611.2 $(M+H)^+$, Anal Calcd for

$C_{33}H_{27}Cl_2N_5O_3$: C, 64.71; H, 4.44; N, 11.43; Found: C, 64.86; H, 4.60; N, 11.64.

4,4′-[(1-Allyl-quinolin-2-one)methylene]bis[3-methyl-1-(3-chlorophenyl)-1H-pyrazol-5-ol] ***6c*** White solid, yield 93 %, 667 mg, mp 184–186 °C; $R_f = 0.54$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,421, 3,069, 2,924, 1,642, 1,592, 1,423, 1,291, 1,058, 881, 798, 768, 692; ^1H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 6H, 2 CH_3), 4.95 (d, $J = 2.0$ Hz, 2H, CH_2), 5.05 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.16 (d, $J = 10.0$ Hz, 1H, the other of $=CH_2$), 5.19 (s, 1H, CH), 6.00 (m, 1H, CH), 7.09-8.17 (m, 13H, Ar–H), 12.45 (s, 1H, OH), 14.21 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 13.43 (CH_3), 30.35 (CH), 44.77 (CH_2), 115.12, 117.56 ($=CH_2$), 119.18, 120.21, 121.67, 127.53, 128.46, 129.28, 130.49, 131.29, 131.84, 133.37, 135.41, 135.87, 137.23, 138.58, 141.39, 147.42, 152.17 (arom.), 161.34 (C = O); ESI–MS: *m/z*: 611.2 $(M+H)^+$, Anal Calcd for $C_{33}H_{27}Cl_2N_5O_3$: C, 64.71; H, 4.44; N, 11.43; Found: C, 64.40; H, 4.14; N, 11.60.

4,4′-[(1-Allyl-quinolin-2-one)methylene]bis[3-methyl-1-(2,5-dichlorophenyl)-1H-pyrazol-5-ol] ***6d*** White solid, yield 94 %, 751 mg, mp 202–204 °C; $R_f = 0.68$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,416, 3,071, 2,918, 1,639, 1,598, 1,421, 1,296, 1,063, 894, 787, 753, 667; ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 6H, 2 CH_3), 4.96 (m, 3H, CH_2 and one of $=CH_2$), 5.17 (m, 2H, the other of $=CH_2$ and CH), 5.96 (m, 1H, CH), 7.17–8.12 (m, 11H, Ar–H), 12.67 (s, 1H, OH), 14.21 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 13.94 (CH_3), 29.66 (CH), 45.13 (CH_2), 115.82, 117.23 ($=CH_2$), 118.61, 126.08, 127.62, 128.26, 129.15, 129.56, 130.13, 130.85, 131.59, 132.94, 133.72, 135.12, 136.18, 138.72, 141.62, 147.29, 151.91 (arom.), 162.15 (C=O); ESI–MS: *m/z*: 680.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{25}Cl_4N_5O_3$: C, 58.17; H, 3.70; N, 10.28; Found: C, 58.01; H, 3.92; N, 10.54.

4,4′-[(1-Allyl-7-chloroquinolin-2-one)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) ***6e*** White solid, yield 92 %, 592 mg, mp 218–220 °C; $R_f = 0.55$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,412, 3,061, 2,927, 1,631, 1,591, 1,417, 1,288, 1,021, 881, 828, 765, 665; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, 2 CH_3), 4.90 (d, $J = 2.0$ Hz, 2H, CH_2), 4.99 (d, $J = 17.6$ Hz, 1H, one of $=CH_2$), 5.12 (d, $J = 10.0$ Hz, 1H, the other of $=CH_2$), 5.13 (s, 1H, CH), 5.92 (m, 1H, CH), 7.13–7.98 (m, 14H, Ar–H), 12.51 (s, 1H, OH), 14.23 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 12.16 (CH_3), 29.27 (CH), 44.44 (CH_2), 116.23, 117.12 ($=CH_2$), 120.25, 121.78, 122.23, 126.56, 128.08, 128.81, 129.67, 130.34, 131.56, 133.54, 135.62, 136.04, 138.64, 147.18, 152.05 (arom.), 161.19 (C=O); ESI–MS: *m/z*: 578.2 $(M+H)^+$, Anal Calcd for $C_{33}H_{28}ClN_5O_3$: C, 68.57; H, 4.88; N, 12.12; Found: C, 68.71; H, 4.71; N, 12.31.

4,4′-[(1-Allyl-7-chloroquinolin-2-one)methylene]bis[3-methyl-1-(2-chlorophenyl)-1H-pyrazol-5-ol] ***6f*** White solid, yield 91 %, 658 mg, mp 192–194 °C; $R_f = 0.48$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,421, 3,068, 2,922, 1,637, 1,597, 1,411, 1,293, 1,025, 893, 821, 758, 690; ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, 2 CH_3), 4.89 (m, 3H, CH_2 and one of $=CH_2$), 5.11 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 5.14 (s, 1H, CH), 5.92 (m, 1H, CH), 7.26–7.95 (m, 12H, Ar–H), 12.57 (s, 1H, OH), 14.11 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 13.05 (CH_3), 29.23 (CH), 45.03 (CH_2), 116.71, 117.65 ($=CH_2$), 118.94, 122.54, 127.57, 128.85, 129.67, 130.65, 131.04, 131.56, 132.21, 132.89, 133.45, 135.68, 136.57, 138.56, 140.45, 147.32, 153.33 (arom.), 161.36 (C=O); ESI–MS: *m/z*: 646.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{26}Cl_3N_5O_3$: C, 61.26; H, 4.05; N, 10.83; Found: C, 61.07; H, 4.23; N, 10.69.

4,4′-[(1-Allyl-7-chloroquinolin-2-one)methylene]bis[3-methyl-1-(3-chlorophenyl)-1H-pyrazol-5-ol] ***6g*** White solid, yield 93 %, 673 mg, mp 202–204 °C; $R_f = 0.57$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,419, 3,071, 2,921, 1,636, 1,595, 1,412, 1,292, 1,026, 897, 825, 769, 672; ^1H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, 2 CH_3), 4.95 (d, $J = 2.0$ Hz, 2H, CH_2), 5.01 (d, $J = 16.8$ Hz, 1H, one of $=CH_2$), 5.14 (d, $J = 10.0$ Hz, 1H, the other of $=CH_2$), 5.17 (s, 1H, CH), 5.92 (m, 1H, CH), 7.12-8.07 (m, 12H, Ar–H), 12.59 (s, 1H, OH), 14.34 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 12.39 (CH_3), 30.43 (CH), 45.67 (CH_2), 116.43, 117.67 ($=CH_2$), 118.56, 119.98, 122.54, 127.69, 128.56, 130.04, 131.67, 132.79, 133.67, 134.78, 135.57, 136.89, 137.09, 138.43, 140.21, 147.11, 153.59 (arom.), 161.20 (C=O); ESI–MS: *m/z*: 646.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{26}Cl_3N_5O_3$: C, 61.26; H, 4.05; N, 10.83; Found: C, 61.56; H, 4.28; N, 11.03.

4,4′-[(1-Allyl-7-chloroquinolin-2-one)methylene]bis[3-methyl-1-(2,5-dichlorophenyl)-1H-pyrazol-5-ol] ***6h*** White solid, yield 92 %, 737 mg, mp 198–200 °C; $R_f = 0.78$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,418, 3,066, 2,921, 1,633, 1,594, 1,423, 1,287, 1,018, 893, 819, 792, 656; ^1H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 6H, 2 CH_3), 4.97 (d, $J = 2.0$ Hz, 2H, CH_2), 5.04 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.18 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 5.19 (s, 1H, CH), 5.96 (m, 1H, CH), 7.18–8.23 (m, 10H, Ar–H), 12.56 (s, 1H, OH), 14.32 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 14.01 (CH_3), 30.29 (CH), 46.48 (CH_2), 116.23, 117.78 ($=CH_2$), 119.62, 126.67, 127.45, 128.87, 129.45, 130.48, 130.93, 132.89,

133.65, 133.94, 135.73, 136.64, 137.03, 138.23, 141.54, 147.62, 152.28 (arom.), 162.04 (C=O); ESI–MS: *m/z*: 714.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{24}Cl_5N_5O_3$: C, 55.37; H, 3.38; N, 9.78; Found: C, 55.04; H, 3.13; N, 9.97.

1-Allyl-3-(3,5-dimethyl-1,7-diphenyl-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7a*** White solid, yield 87 %, 536 mg, mp 244–246 °C; $R_f = 0.56$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,061, 2,925, 1,631, 1,582, 1,492, 1,307, 1,026, 987, 792, 723, 692; ^1H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 6H, 2 CH_3), 4.94 (d, $J = 1.6$ Hz, 2H, CH_2), 4.96 (d, $J = 17.6$ Hz, 1H, one of $=CH_2$), 5.11 (s, 1H, CH), 5.16 (d, $J = 10.8$ Hz, 1H, the other of $=CH_2$), 5.97 (m, 1H, CH), 7.17-8.00 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.24 (CH_3), 27.89 (CH), 44.30 (CH_2), 113.21.37, 117.42 ($=CH_2$), 120.51, 121.72, 122.58, 126.31, 128.37, 129.17, 129.59, 130.65, 130.74, 132.77, 133.63, 135.52, 138.92, 147.48, 149.85 (arom.), 162.12 (C=O); ESI–MS: *m/z*: 526.2 $(M+H)^+$,Anal Calcd for $C_{33}H_{27}N_5O_2$: C, 75.41; H, 5.18; N, 13.32; Found: C, 75.64; H, 5.47; N, 13.04.

1-Allyl-3-(3,5-dimethyl-1,7-bis(2-chlorophenyl)-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7b*** White solid, yield 85 %, 592 mg, mp 236–238 °C; $R_f = 0.54$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,066, 2,921, 1,634, 1,579, 1,496, 1,313, 1,024, 982, 790, 749, 688; ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, 2 CH_3), 4.91 (m, 3H, CH_2 and one of $=CH_2$), 5.11 (m, 2H, the other of $=CH_2$ and CH), 5.94 (m, 1H, CH), 7.21–7.97 (m, 13H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 12.32 (CH_3), 27.54 (CH), 44.51 (CH_2), 112.31, 116.59 ($=CH_2$), 119.99, 122.55, 127.94, 128.34, 128.95, 130.28, 130.49, 130.77, 131.03, 132.00, 132.73, 133.11, 135.55, 138.31, 140.39, 147.06, 153.25 (arom.), 161.62 (C=O); ESI–MS: *m/z*: 593.1 $(M+H)^+$,Anal Calcd for $C_{33}H_{25}Cl_2N_5O_2$: C, 66.67; H, 4.24; N, 11.78; Found: C, 66.33; H, 4.56; N, 12.01.

1-Allyl-3-(3,5-dimethyl-1,7-bis(3-chlorophenyl)-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7c*** White solid, yield 88 %, 613 mg, mp 240–242 °C; $R_f = 0.61$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,071, 2,928, 1,633, 1,586, 1,491, 1,321, 1,019, 978, 791, 761, 663; ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, 2 CH_3), 4.94 (m, 3H, CH_2 and one of $=CH_2$), 5.14 (m, 2H, the other of $=CH_2$ and CH), 5.94 (m, 1H, CH), 7.18–7.95 (m, 13H, Ar–H), ^{13}C NMR (100 MHz, DMSO-d_6): 13.84 (CH_3), 28.10 (CH), 44.61 (CH_2), 112.53, 117.83 ($=CH_2$), 118.58, 119.93, 121.47, 127.95, 128.42, 129.65, 130.13, 131.23, 131.69, 133.75, 135.37, 135.80, 137.60, 138.53, 141.31, 147.75, 150.11 (arom.), 161.27 (C=O); ESI–MS: *m/z*: 593.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{25}Cl_2N_5O_2$: C, 66.67; H, 4.24; N, 11.78; Found: C, 66.65; H, 4.04; N, 11.63.

1-Allyl-3-(3,5-dimethyl-1,7-bis(2,5-dichlorophenyl)-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7d*** White solid, yield 87 %, 677 mg, mp 252–254 °C; $R_f = 0.72$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,062, 2,925, 1,632, 1,584, 1,501, 1,324, 1,020, 991, 782, 678; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, 2 CH_3), 4.93 (d, $J = 2.0$ Hz, 2H, CH_2), 4.95 (d, $J = 17.2$ Hz, 1H, one of $=CH_2$), 5.11 (s, 1H, CH), 5.15 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 5.95 (m, 1H, CH), 7.22-8.04 (m, 11H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.54 (CH_3), 28.02 (CH), 44.97 (CH_2), 113.24, 117.79 ($=CH_2$), 118.65, 126.56, 128.14, 128.84, 129.65, 130.16, 130.78, 131.57, 132.07, 132.89, 133.94, 135.34, 136.81, 139.23, 141.75, 147.64, 151.01 (arom.), 161.63 (C=O); ESI–MS: *m/z*: 662.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{23}Cl_4N_5O_2$: C, 59.75; H, 3.49; N, 10.56; Found: C, 59.73; H, 3.30; N, 10.36.

1-Allyl-7-chloro-3-(3,5-dimethyl-1,7-diphenyl-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7e*** White solid, yield 89 %, 557 mg, mp 236–238 °C; $R_f = 0.62$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,062, 2,926, 1,637, 1,582, 1,496, 1,309, 1,021, 989, 829, 757, 667; ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, 2 CH_3), 4.93 (m, 3H, CH_2 and one of $=CH_2$), 5.11 (s, 1H, CH), 5.14 (d, $J = 12.0$ Hz, 1H, the other of $=CH_2$), 5.91 (m, 1H, CH), 7.24–8.01 (m, 14H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.65 (CH_3), 27.86 (CH), 45.17 (CH_2), 112.69, 118.02 ($=CH_2$), 120.05, 121.64, 122.54, 125.92, 128.34, 128.95, 129.34, 130.49, 131.75, 133.27, 136.11, 136.88, 138.79, 147.42, 150.06 (arom.), 161.37 (C=O); ESI–MS: *m/z*: 560.2 $(M+H)^+$, Anal Calcd for $C_{33}H_{26}ClN_5O_2$: C, 70.77; H, 4.68; N, 12.50; Found: C, 70.98; H, 4.82; N, 12.75.

1-Allyl-7-chloro-3-(3,5-dimethyl-1,7-bis(2-chlorophenyl)-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7f*** White solid, yield 86 %, 605 mg, mp 256–258 °C; $R_f = 0.56$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,063, 2,931, 1,641, 1,586, 1,486, 1,325, 1,029, 991, 824, 792, 657; ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, 2 CH_3), 4.90 (d, $J = 2.0$ Hz, 2H, CH_2), 4.99 (d, $J = 17.6$ Hz, 1H, one of $=CH_2$), 5.12 (m, 2H, the other of $=CH_2$ and CH), 5.93 (m, 1H, CH), 7.21–7.99 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 12.93 (CH_3), 28.21 (CH), 44.23 (CH_2), 113.17, 117.72 ($=CH_2$), 119.12, 122.42, 127.31, 128.64, 129.93, 130.42, 131.32, 131.28, 132.75, 132.81, 133.39, 135.59, 136.26, 138.91, 140.81, 147.16, 149.62 (arom.), 161.63 (C=O); ESI–MS: *m/z*: 628.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{24}Cl_3N_5O_2$: C, 63.02; H, 3.85; N, 11.14; Found: C, 63.28; H, 3.56; N, 10.84.

1-Allyl-7-chloro-3-(3,5-dimethyl-1,7-bis(3-chlorophenyl)-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7g*** White solid, yield 85 %, 709 mg, mp 236–238 °C; $R_f = 0.62$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,072, 2,928, 1,641, 1,584, 1,487, 1,301, 1,019, 992, 827, 772, 676; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, 2 CH_3), 4.93 (m, 3H, CH_2 and one of $=CH_2$), 5.09 (s, 1H, CH), 5.13 (d, $J = 10.8$ Hz, 1H, the other of $=CH_2$), 5.91 (m, 1H, CH), 7.23–7.99 (m, 12H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 12.56 (CH_3), 28.31(CH), 44.38 (CH_2), 113.32, 117.59 ($=CH_2$), 118.46, 119.32, 122.63, 127.36, 128.92, 130.36, 131.39, 132.46, 133.63, 134.27, 135.47, 136.73, 137.32, 138.64, 140.63, 147.55, 150.14 (arom.), 161.48 (C=O); ESI–MS: *m/z*: 628.1 $(M+H)^+$, Anal Calcd for $C_{33}H_{24}Cl_3N_5O_2$: C, 63.02; H, 3.85; N, 11.14; Found: C, 63.34; H, 4.03; N, 11.34.

1-Allyl-7-chloro-3-(3,5-dimethyl-1,7-bis(2,5-dichlorophenyl)-1,4-dihydro-1H-dipyrazolo[3,4-b:4′3′-e]pyran-4-yl)quinoline-2-one ***7h*** White solid, yield 88 %, 687 mg, mp 228–230 °C; $R_f = 0.82$ (ethyl acetate/*n*-hexane 9.5:0.5); IR (ν_{max}, cm^{-1}): 3,063, 2,922, 1,639, 1,567, 1,493, 1,309, 1,026, 991, 828, 786, 665; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, 2 CH_3), 4.96 (d, $J = 1.6$ Hz, 2H, CH_2), 5.04 (d, $J = 17.6$ Hz, 1H, one of $=CH_2$), 5.10 (s, 1H, CH), 5.18 (d, $J = 10.4$ Hz, 1H, the other of $=CH_2$), 5.94 (m, 1H, CH), 7.21-8.30 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.58 (CH_3), 27.91 (CH), 45.38 (CH_2), 112.78, 117.81 ($=CH_2$), 119.72, 126.43, 127.81, 128.92, 129.26, 130.56, 130.72, 132.82, 133.64, 134.31, 135.84, 136.62, 137.59, 138.46, 141.38, 147.61, 150.18 (arom.), 161.85 (C=O); ESI–MS: *m/z*: 696.0 $(M+H)^+$, Anal Calcd for $C_{33}H_{22}Cl_5N_5O_2$: C, 56.80; H, 3.18; N, 10.04; Found: C, 56.96; H, 3.34; N, 9.81.

Conclusions

In conclusion, we have developed a new recyclable TBA–HS catalyzed one-pot procedure for quinolylmethelene-bispyrazoles via a tandem Knoevenagel–Michael reaction under solvent-free conditions. Main advantage of the method is that chromatography was not used to isolate the desired product. Temperature- and stoichiometry-controlled nature of the products is other interesting part. While, equal amount of reactants yielded Knoevenagel-adducts at 100 °C, doubling the amount of one of the reactants pyrazolone with aldehyde resulted into formation of Knoevenagel–Michael-adducts. Heating the mixture at 120 °C, however, resulted in the cyclization of Michael-adducts and gave dipyrazolopyranylquinolines. Biological screening tests results revealed that all newly synthesized compounds possess antibacterial and antitubercular activities. Specifically, **7d** resembles standard drug ciprofloxacin in terms of its potency against *Streptococcus pneumoniae* bacteria. Compounds **5a** and **5f** on the other hand are very close to standard fluconazole (>256 μg/mL) and miconazole (>256 μg/mL) in their antitubercular activity, showing percent growth inhibitions in the 91–92 % range.

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