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ORIGINAL ARTICLE

Classical and microwave assisted synthesis of new 4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-ylazo)-*N*-(2-substituted-4-oxo-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives and their antimicrobial activities

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Abstract A simple and efficient methodology was developed for the synthesis of new 4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-ylazo)-*N*-(2-substituted-4-oxo-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives **10a**–**10j** in good amount of yields. They have been prepared using 2-acetamidobenzoic acid derivatives **2a**–**2j** via intermediates benzenesulfonamide substituted quinazolinone derivatives **8a**–**8j**, and its corresponding hydrazono derivatives **9a**–**9j**. Entitled compounds (**10a**–**10j**) were also obtained using microwave heating in good amount of yields. The structures of all the new compounds have been evaluated on the basis of elemental analysis, FT-IR, ^{1}H and ^{13}C NMR spectral studies. Entitle compounds have been screened for their *in vitro* antimicrobial activities and all these compounds displayed excellent to moderate activities, which were found to be significantly potent against bacteria compared to fungal.

1. Introduction

Perusal of literature survey reveals that the quinazolinone skeleton is found in a number of biologically active molecules. There are various reports regarding substitution at 2nd and/or 3rd position of quinazolinone skeleton. Specifically, 4(3*H*)-quinazolinone derivatives display a broad range of

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biological properties such as antihypertensive (Haruhisa et al., 2006), CNS depressant (Kashaw et al., 2009; Saber et al., 2007), antitumor, analgesic and anti-inflammatory, antibacterial and antifungal activities (Pandey et al., 2009; Laddha et al., 2006; Sondhi et al., 2010). Octahydroquinazolinone derivatives have exhibited potent antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* (Kidwai et al., 2005) and calcium antagonist activity (Yarim et al., 2002, 2003; Kantevari et al., 2006). These classes of compounds have also shown interference with insulin secretion and smooth muscle contractile channel activity (Somers et al., 2001). On the other hand, various therapeutic activities have also been reported for the pyrazole moieties (Hong et al., 2009; Badawey and El-Ashmawey, 1998; Bailey et al., 1985). However, there are no such reports in which both quinazolinone and pyrazole rings are linked by benzenesulfonamide substituted hydrazono bridge. Therefore, it was thought interesting to bring the above two moieties within a single molecular framework to afford their additive biological properties. Thus, the present communication comprises synthesis, characterization and antimicrobial activities of newer 4-(3,5-dimethyl -1-phenyl-1*H*-pyrazol-4-ylazo)-*N*-(2-substituted-4-oxo-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives **10a**–**10j**.

2. Results and discussion

2.1. Chemistry

Majority of the reported 4(3*H*)-quinazolinone derivatives were synthesized either from anthranilic acid or its derivatives (Hisano, 1973) (shown in Scheme 1). There are very few reports (Zahran, 2000; Gupta et al., 1988; Morsy, 2007) regarding preparation of the compound **6a**, expect our recently reported work [**8a**–**8j**] (Jagani et al., 2011). The reported methods for the synthesis of compound **6a** involve the sulfonylation of 3-aminoquinazolinone (**4**) using *p*-acetamidobenzenesulfonylchloride (**5**) under reflux condition in the presence of base (i.e. pyridine or NaOH) as shown in Scheme 1 (yields were in the range of 58 to 66%). In another report (Yuefen et al., 2004), compound **6a** was prepared using 2-methyl-4*H*-3,1-benzoxazin-4-one (**3**) and *N*-[4-(hydrazinosulfonyl)phenyl] acetamide (**7**) as shown in Scheme 1.

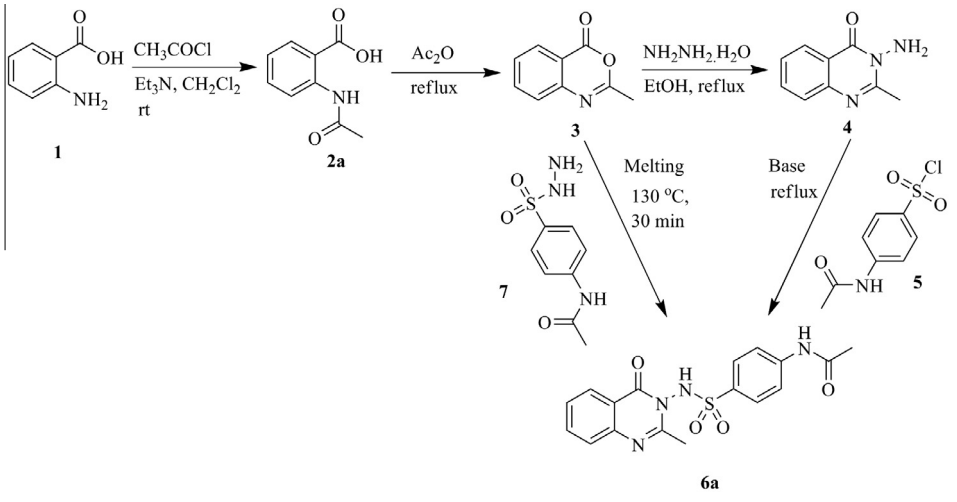
The above methods proceed via highly moisture sensitive, irritant, and electronically unsaturated character of unstable 2-methyl-4*H*-3,1-benzoxazin-4-one (**3**) bearing substitution at second position which renders them difficult to synthesize (Madkour, 2005). In addition to this, more number of synthetic steps decreases the overall yield.

To overcome such problems, we have established the reaction pathway for the synthesis of 4-amino-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide **8a** and its derivatives (**8a**–**8j**) (Jagani et al., 2011), which was again optimized by changing reaction conditions to prepare the same compounds and is shown in Scheme 2. The structure of compounds **8a**–**8j** was confirmed by mass spectra and melting point.

4-[*N*′-(1-Acetyl-2-oxo-propylidene)hydrazino]-*N*-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives **9a**–**9j** were prepared starting from 4-amino-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide **8a**–**8j**, and is shown in Scheme 3.

Pyrazole derivatives (**10a**–**10j**) were prepared via both classical and microwave irradiation from hydrazono compounds (**9a**–**9j**), as shown in Scheme 3. Comparisons of both synthetic approaches have been displayed in Table 1, which showed optimization of reaction time and an increase in yields under microwave condition.

The structure of compounds **9a**–**9j** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra and the characterization of **9a** is included herewith (Pavia et al., 2008). The IR spectrum of **9a** showed the presence of C=O group at 1695 cm^{-1} due to CONH and $COCH_3$ groups. Two sharp bands at 1324 and 1142 cm^{-1} were due to asymmetric and symmetric stretching vibrations of SO_2 group, respectively. The two bands at 1510 and 1550 cm^{-1} were due to N—H bending of secondary amine and sulfonamide groups respectively. The ^{1}H NMR of **9a** showed a singlet at δ 10.91 ppm due to highly deshielded proton of $NHSO_2$ group. One singlet was observed at δ 9.11 ppm due to secondary amine group. The two more singlets appeared in the aliphatic region at δ 2.51 and 2.25 ppm due to $COCH_3$ and CH_3 protons at second position of the quinazolinone ring respectively. All the 8 aromatic protons resonated



Scheme 1 General routes of synthesis of quinazolin-4(3*H*)-one.