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REVIEW

2nd Heterocyclic Update

Overview on the recently developed coumarinyl heterocycles as useful therapeutic agents

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Abstract The chemical class of benzopyrones consists of a large number of compounds possessing the *benzene ring* fused with the oxygen containing *pyrone ring*. This class is further divided into the *benzo-γ-pyrone* i.e. flavonoids and the *benzo-α-pyrone* i.e. coumarins. Coumarins, the 2*H*-chromen-2-one and its related analogues exhibit a multitude of biological activities. Attempts made in the continuous chemical diversification of this parent nucleus have brought significant alterations in the biological activity among the generated compounds and therefore, this category of benzopyrones has been much exploited in the current medicinal chemistry research. Thus, it was thought worthwhile to present a review on the newly synthesised heterocyclic coumarinyl derivatives with their physicochemical parameters and biological activity, attempted by our co-workers. This review also creates a platform for highlighting approaches and strategies used in the chemical synthesis of coumarinyl compounds along with their biological activity relating to their structure.

Abbreviations: MIC, minimum inhibitory concentration; *Log p*, partition coefficient; *Pka*, dissociation constant

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Contents

1. Introduction

Coumarin and its related analogues are found to occur naturally as secondary metabolites in higher plants (Curir et al., 2007 and Lee, 2004) and also in micro-organisms (Xu et al., 2009). Simple compounds belonging to this chemical class, for instance 7-hydroxy coumarin (Fylaktakidou et al., 2004) and 4-hydroxy coumarin (Jung and Park, 2009) have been used as a backbone to attain chemically and biologically diverse agents. Some of the extensions made on the parent coumarin have generated newer chemical compounds which act against various targets like bacterial DNA *gyrase* (Musicki et al., 2003) and *topoisomerase* (Peng and Marians, 1993), *monoamine oxidase* (Chimenti et al., 2009), *acetylcholinesterase* (Anand et al., 2012), TNF-α (N Noolvi et al., 2011), IL-6 (Upadhyay et al., 2011), ROS pathway (Beillerot et al., 2008), macrophage migration inhibitory factor (MIF) (Orita et al., 2001), *casein kinase* 2 (CK2) (Chilin et al., 2008), *serine protease* (Pochet et al., 1996), *tyrosinase* (Fais et al., 2009), 5α-*reductase* (Fan et al., 2001), 17β-*hydroxysteroid dehydrogenase* type-1, *oxidoreductase*, *cyclooxygenase* and *lipoxygenase* (Geronikaki et al., 2008). In recent years, many structural modifications have been attempted at various positions of the coumarin ring system, Fig. A.1, (Anand et al., 2012; Beillerot et al., 2008 and Chilin et al., 2008) for example, at the **2nd** position (Liu et al., 2006), **3rd** position (Musa et al., 2011; Nikhilet al., 2012 and Sashidhara et al., 2011), **4th** position (Jung and Park, 2009), **5th** position (Noolvi et al., 2011), **6th** position (Starcevic et al., 2011), **7th** position (Manojkumar et al., 2009) and the **8th** position (Eissa et al., 2009). Some of the other modifications include, formation of coumarinyl metal complexes (Kostova and Momekov, 2006), synthesis of thiocoumarin (Kumar et al., 2005 and Reddy et al., 2005) and iminocoumarin analogues (Gorobets et al., 2002). Moreover, the increase in the number of coumarin derivatives synthesised and screened for biological activity has made it essential to study compounds under this chemical class as, such scaffolds possess significant therapeutic potentials. Thus, in this review we focus on some of the modifications attempted on the coumarin ring by our team over a period of time and discuss various synthetic approaches, physicochemical parameters and biological activity studies.

2. Synthesis of coumarin analogues

Coumarin and its related derivatives have been well reported to be synthesised via various mechanisms involved in reactions such as Claisen rearrangement (Ghantwal and Samant, 1999), Perkin reaction (Majumder and Majumder, 1993), Pechmann reaction (Upadhyay et al., 2008), Witting reaction (Harayama et al., 1994), Knoevenagel condensation (Shaabani et al., 2009) and Baylis–Hillman Reaction (Musa, 2002). In recent years, attempts have been made to prepare coumarinyl derivatives by other alternative methods such as solid phase synthesis (Liu et al., 2006), microwave irradiation (Kidwai et al., 2004) and ultrasonication (Di Cuollo et al., 1965). Further, the synthesis of coumarin hybrid with resveratrol (Fais et al., 2009) and estrogen (Musa et al., 2009) was among some of the strategies applied to arrive at potential therapeutic agents. In this review, we summarise various approaches used for the synthesis of different conjugated coumarin-heterocyclic ring systems by our team.

2.1. Combination of thiazole ring and coumarin nucleus

Thiazoles have been extensively used in various chemical reactions as a parent, substituent as well as an intermediate